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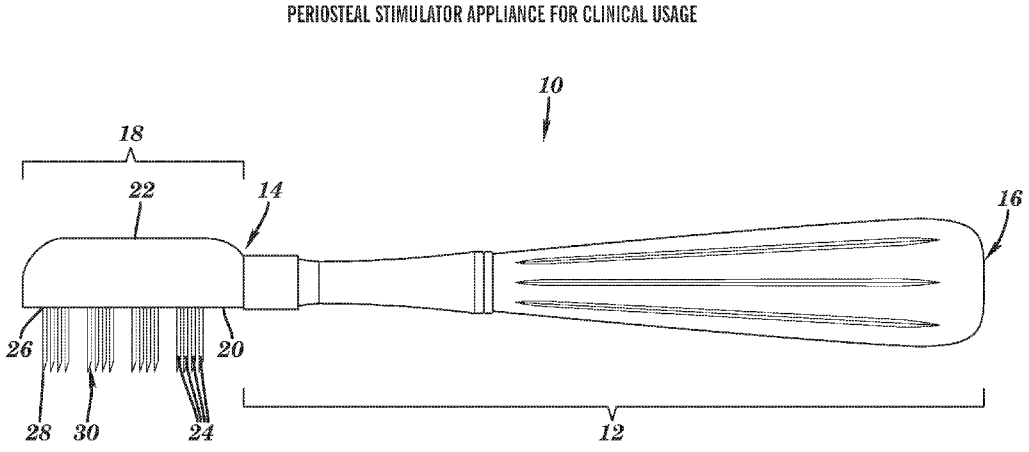

FIG. 1A

(57) Abstract: The present invention relates to a device. The device includes an elongate handle having a proximal end and a distal end; a head portion extending from the proximal end of the elongate handle, the head portion having a first interior-facing surface and an opposing second exterior-facing surface; and a plurality of microneedles extending from, and perpendicular to, the first interior-facing surface of the head portion. Each of the plurality of microneedles has a base connected to the first interior-facing surface of the head portion and a free tip end. The present invention also relates to a method for stimulation of cortical bone formation using the device of the present invention.

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BONE GROWTH STIMULATOR AND METHODS OF USE

[0001] This application claims priority benefit of U.S. Provisional Patent Application No. 62/546,799, filed August 17, 2017, which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0001] The present invention relates to devices and methods of their use in stimulating bone formation.

BACKGROUND OF THE INVENTION

[0002] One of the main challenges in orthodontics relates to the cortical bone that surrounds the alveolar bone. This bone acts as an envelope that determines the limit to which a tooth can be moved safely. Since cortical bone does not follow the moving tooth, any movement towards that cortical plate may push the tooth out of the bone envelope. This may cause bone loss around the tooth, which can jeopardize the long term prognosis of the tooth. To compensate for this limitation, many extensive and expensive surgical approaches have been proposed to cut the bone and tooth together as a segment and move the tooth and the surrounding cortical bone surgically. Due to the complexity of these procedures, many adults prefer to not go through surgery and therefore never accomplish proper orthodontic correction.

[0003] In addition, the major limitation of orthodontic corrections in patients with mild to moderate skeletal deformities is the inability to move teeth beyond the confines of the cortical bone to compensate for the jaws discrepancy and provide a functional occlusion. Therefore, there is no alternative treatment modality to surgical correction of skeletal problems, leaving patients no option but to adopt less functional bites, sacrifice teeth for an incomplete dental compensation of jaws discrepancies, and settle for less than optimum treatment outcomes.

[0004] Skeletal problems can occur in three planes of space (vertical, sagittal, and transverse) and the prevalence can vary with ethnicity, being as high as 22.5% for class II and 12.6% for class III (*see* Silva et al. "Prevalence of Malocclusion Among Latino Adolescents," *Am. J. Orthod. Dentofacial Orthop.* 119(3):313-315 (2001)), 3% for open bites, and even a larger percentage of the population (i.e., 9.1%) present

narrow deficient jaws (*see* Brunelle et al., "Prevalence and Distribution of Selected Occlusal Characteristics in the US Population, 1988-1991," *J. Dent. Res.* 75(2 Suppl.): 706-713 (1996)). To help the growing population of adults seeking orthodontic treatment, there is an enormous need for a technique that can stimulate bone formation at the surface of cortical bone non-invasively. Such a technique would dramatically expand the limit of orthodontic dental corrections.

[0005] The present invention is directed to overcoming these and other deficiencies in the art.

SUMMARY OF THE INVENTION

[0006] One aspect of the present invention relates to a device. The device includes an elongate handle having a proximal end and a distal end; a head portion extending from the proximal end of the elongate handle, the head portion having a first interior-facing surface and an opposing second exterior-facing surface; and a plurality of microneedles extending from, and perpendicular to, the first interior-facing surface of the head portion. Each of the plurality of microneedles has a base connected to the first interior-facing surface of the head portion and a free tip end.

[0007] Another aspect of the present invention relates to a method for stimulation of cortical bone formation. The method involves providing a device. The device includes an elongate handle having a proximal end and a distal end; a head portion extending from the proximal end of the elongate handle, the head portion having a first interior-facing surface and an opposing second exterior-facing surface; and a plurality of microneedles extending from, and perpendicular to, the first interior-facing surface of the head portion. Each of the plurality of microneedles has a base connected to the first interior-facing surface of the head portion and a free tip end. The method also involves positioning the free tip end of said plurality of microneedles in contact with tissue of a subject, where cortical bone underlies the subject's tissue. The method further involves applying pressure to the device to cause the microneedles to penetrate the subject's tissue without penetrating the cortical bone underlying the subject's tissue, thereby stimulating formation of cortical bone underlying the subject's tissue.

[0008] The form of the skeleton is dictated by cortical bone, and the density of bone is dictated by both trabecular and cortical bone. While there are non-invasive

methods to increase trabecular bone density, there are none that can change the shape or form of cortical bone without aggressive surgical intervention. As described *infra,* the present invention represents a new treatment methodology for treating skeletal defects using a minimally invasive method by stimulating craniofacial cortical bone formation in the desired direction. The ability to drift the cortical bone in a desired direction will expand the biological envelope, range, and distance to which teeth can be moved orthodontically allowing non-surgical correction of severe malocclusions resulting from severe skeletal deformities.

[0009] The device and method of the present invention may be used to stimulate cortical bone formation at the surface of cortical bone (e.g., craniofacial bone), restore bone shape in bone deformity and deficient areas, stimulate new bone formation and cortical drift in the direction of force on bone (e.g., in the direction of tooth movement or jaw expansion), expand the range of tooth movement and orthopedic corrections in growing and non-growing subjects, and change the shape of the craniofacial bones to improve facial aesthetics. Corrections made possible with the device and method of the present invention include expansion of jaws, vertical jaw development, sagittal correction of dentoalveolar discrepancies, modelling of facial bones, and correction of bone defects due to syndromes (cleft palate) or pathology (periodontal disease, extractions). Currently, orthopedic corrections are an accepted treatment modality only for growing patients. The present invention establishes a new field of adult dentofacial orthopedic treatment in non-growing patients.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] Figures 1A-1F are schematic illustrations of embodiments of a device according to the present invention. Figure 1A is a side perspective view of a first embodiment of a device according to the present invention. Figures 1B and 1C are bottom and side views, respectively, of a second embodiment of a device according to the present invention. Figures 1D and 1E are cross-sectional, side views of two additional embodiments of the present invention including a chamber (fluid reservoir or compartment) within the device. Figure 1F is a cross-sectional, side view of a further embodiment of a device according to the present invention including a chamber (fluid reservoir or compartment) within the device and a loading channel

(exterior port) that permits filling of the compartment with a composition including, e.g., exogenous growth factors.

[0011] Figures 2A-2C show an embodiment of manually loading a composition including, e.g., exogenous growth factors into a compartment within a device of the present invention (Figures 2A-2B) via a port (or channel) suitable to receive a pipette tip (shown), needle tip, or the like. This embodiment facilitates injection of the composition (including, e.g., exogenous growth factors) to the area of interest by, e.g., applying pressure to the device to thereby expel the composition through microneedles of the device (Figure 2C, arrow representing pressure).

[0012] Figures 3A and 3B are schematic illustrations of a further embodiment of a device according to the present invention. This embodiment is similar to the embodiment shown in Figures 2A-2C, but does not include a port for manual loading by, e.g., pipette or needle. This device may be pre-loaded (e.g., in manufacturing the device) with the composition of interest to facilitate the procedure for clinician. Like the embodiment shown in Figures 2A-2C, this embodiment allows delivery of the composition (including, e.g., exogenous growth factors) to the area of interest by, e.g., applying pressure to the device (shown with an arrow in Figures 3A and 3B) to expel the composition through microneedles of the device (shown in Figure 3B).

[0013] Figures 4A-4D are schematic illustrations showing a method of using a device according to the present invention relative to the soft tissue and bone of an area of treatment of a subject. The device is positioned relative to the area of interest having soft tissue (e.g., gingiva and periosteum) with underlying cortical bone (Figure 4A). Pressure is applied to the device suitable to cause microneedles to penetrate the **subject's soft tissue without penetrating** underlying cortical bone (Figures 4B and 4C) and the device is then withdrawn (Figure 4D). This penetration of the soft tissue without penetration of the underlying cortical bone stimulates local release of endogenous growth factors under the periosteum (Figures 4C and 4D), which in turn stimulates cortical bone growth.

[0014] Figure 5 is a schematic illustration showing the result of use of a device like that shown in Figures 3A and 3B, relative to the soft tissue and bone. In this embodiment, a method like that shown in Figures 4A-4D is employed with the additional step of (after penetration of the soft tissue and prior to removing the device) actuating a release mechanism (e.g., via pressure applied to the device, as shown in

Figures 3A and 3B) to release a composition including, e.g., exogenous growth factors from a compartment in the head of the device through the microneedles and into the subject's tissue. As shown, this method therefore involves local injection of exogenous growth factors as well as stimulation of local production of endogenous growth factors.

[0015] Figure 6 is a schematic representation of the effect of periosteal stimulation using a device according to the present invention and resultant stimulation of new cortical bone formation on the surface of the existing cortical bone.

[0016] Figures 7A and 7B are schematic illustrations showing changes in alveolar bone before expansion (Figure 7A) and after expansion (Figure 7B), illustrating of the effect of transverse orthodontic forces (F) on cortical bone in the absence of periosteal stimulation.

[0017] Figures 8A and 8B are schematic illustrations of the effect of orthodontic force (F) and periosteal stimulation (left panels of Figures 8A and 8B, small rectangles) in presence (Figure 8B) and absence (Figure 8A) of exogenous growth factor (left panel of Figure 8B, teardrop shapes). Figure 8A illustrates the effect of periosteal stimulation according to the present invention that stimulates endogenous release of growth factors on the surface of the cortical bone as the tooth moves in response to orthodontic forces. Figure 8B illustrates the synergistic effect of periosteal stimulation according to the present invention that induces release of endogenous growth factors coupled with release of exogenous growth factors during application of orthodontic forces.

[0018] Figures 9A and 9B are a photograph (Figure 9A) and micro-CT image (Figure 9B) from an experimental subject illustrating the orthodontic transverse forces applied to the upper molars of the subject, pushing the molars towards the cortical bone.

[0019] Figures 10A and 10B are micro-CT images of control (no expansion) (Figure 10A) and expansion (Figure 10B) subjects collected after 56 days. In response to orthodontic forces, teeth were moved towards the cortical bone (Figure 10B). As shown, the bone did not follow the tooth and, therefore, bone loss around the roots of the tooth was apparent (Figure 10B, top panel) and the cortical plate became thinner (Figure 10B, bottom panel).

[0020] Figures 11A and 11B are images illustrating the location of periosteal stimulation according to the method of the present invention in an experimental group. In addition to transverse orthodontic forces, animals were exposed to periosteal stimulation around the area of first and second molar (arrows in Figure 11A and dots within the boxed area of Figure 11B) once per week.

[0021] Figures 12A-12C are photographs of embodiments of devices according to the present invention similar to that used to apply periosteal stimulation, as described in the Examples herein.

[0022] Figures 13A and 13B are micro-CT images showing that, after 56 days of expansion treatment with periosteal stimulation according to methods of the present invention, the animals did not show any bone loss (Figure 13A) and their cortical bone did not get thinner (Figure 13B).

[0023] Figures 14A and 14B are fluorescent microscopy images showing significant increase in rate of bone formation in the area of cortical bone for the experimental group receiving expansion and periosteal stimulation (Figure 14B) according to methods of the present invention, as compared to expansion alone (Figure 14A).

[0024] Figures 15A-15C are fluorescent microscopy images showing results of a series of experiments in which animals were divided into 3 groups: 1) control that did not receive any treatment; 2) animals that received injection of PDGF once per week (around first molar area); and 3) animals that received periosteal stimulation according to methods of the present invention once per week in a similar area. No orthodontic force was applied to these animals/teeth. Compared to control (Figure 15A), the group that received injection of PDGF did not show significant bone formation (Figure 15B) while the group that received periosteal stimulation according to methods of the present invention demonstrated significant bone formation (Figure 15C). These results indicate that the endogenous release of growth factors in response to periosteal stimulation according to methods of the present invention is more effective to stimulate bone formation than injection of exogenous growth factors.

[0025] Figures 16A-16C are fluorescent microscopy images showing results of a series of experiments in which groups of animals were exposed to PDGF or periosteal stimulation in presence of orthodontic transverse forces. Fluorescent microscopy demonstrates that PDGF in presence of orthodontic forces was able to

slightly increase the rate of bone formation, but this effect was very apparent in presence of periosteal stimulation according to methods of the present invention (Figures 16A and 16B). To evaluate if injection of exogenous growth factor can have synergic effects on endogenous release of growth factor, in another series of experiments, animals were weekly exposed to both periosteal stimulation according to methods of the present invention and PDGF injection in presence of orthodontic forces. Fluorescent microscopy of these animals demonstrates significant increase in rate of bone formation in response to periosteal stimulation according to methods of the present invention, and demonstrates synergic effect between external and endogenous growth factors (Figure 16C).

DETAILED DESCRIPTION OF THE INVENTION

[0026] One aspect of the present invention relates to a device. The device includes an elongate handle having a proximal end and a distal end; a head portion extending from the proximal end of the elongate handle, the head portion having a first interior-facing surface and an opposing second exterior-facing surface; and a plurality of microneedles extending from, and perpendicular to, the first interior-facing surface of the head portion. Each of the plurality of microneedles has a base connected to the first interior-facing surface of the head portion and a free tip end.

[0027] The device according to the present invention is sometimes referred to herein as device, appliance, periosteal stimulator, periosteal stimulator appliance, bone growth stimulator, or cortical stimulator. It will be understood that such terms each refer to a device according to the present invention.

[0028] Figures 1A-1F are schematic illustrations of embodiments of a device according to the present invention that may be used to, for example, stimulate release of endogenous growth factors around the periosteum under the gum as described herein. This cortical bone stimulation device, in contrast to MOP devices (i.e., **m**icro-**o**steo**p**erforation devices), does not include a portion (e.g., a cutting tip) suitable to penetrate deeply (or at all) into bone. The device of the present invention may be used by a clinician manually under minimum local or topical anesthesia, in areas of interest or treatment, as described in detail below. Like numbers refer to like elements throughout.

[0029] With reference to Figures 1A-1F, the cortical bone stimulation device **10,110, 210** includes an elongate handle **12, 112, 212** having proximal end **14, 114, 214** and a distal end **16, 116, 216**. Handle **12, 112, 212** may be a unitary piece or include multiple separable (or detachable) portions that are joined together (e.g., by threaded engagement (screwing), snapping, or the like) to form elongate handle **12, 112, 212**. Elongate handle **12, 112, 212** may be of any length suitable for easy hand grasp by a user (e.g., clinician). Although shown with a flared design in Figure 1A, it will be understood that elongate handle **12, 112, 212** may be of any suitable shape allowing easy grasp.

[0030] A head portion **18, 118, 218** extends from the proximal end **14, 114, 214** of handle **12, 112, 212**. Head portion **18, 118, 218** and handle **12, 112, 212** may be unitary or separable (detachable) portions that are joined together (e.g., by threaded engagement (screwing), snapping, or the like) to form cortical bone stimulation device **10, 110, 210**. Head portion **18, 118, 218** has a first interior-facing surface **20, 120, 220** and an opposing second exterior-facing surface **22, 122, 222**. In one embodiment, the device is a dental device and head portion **18, 118, 218** is adapted for intra-**oral placement in a subject's mouth.** Head portion **18, 118, 218** may be of any suitable shape including, but not limited to round, ovoid, or rectangular.

[0031] In one embodiment, the exterior-facing surface **22, 122, 222** of the head portion **18, 118, 218** includes a rest **34, 134, 234** (*see* Figures 1C-1F) adapted to receive a thumb or forefinger. The rest **34, 134, 234** may be formed of an elastomeric material and/or any other anti-slip material. Rest **34, 134, 234** may also include projections or the like to prevent slip during use.

[0032] A plurality of microneedles **24, 124, 224** extend from, and are perpendicular to, the first interior-facing surface **20, 120, 220** of head portion **18, 118, 218**. Each of the plurality of microneedles **24, 124, 224** has a base **26, 126, 226** connected to the first interior-facing surface **20, 120, 220** and a free tip end **28, 128, 228**. Cortical bone stimulation device **10, 110, 210** may include, for example, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 27, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, and so on up to 100 or more microneedles **24, 124, 224**. Each of the microneedles **24, 124, 224** has an exterior length from the base **26, 126, 226** to free tip end **28, 128, 228**. As will be understood from reference to, for example, Figures 1D, 1E, and 1F,

each of the microneedles **24, 124, 224** may have a further portion or length terminating at an interior end **27, 127, 227** (*see, e.g.,* Figures 1D, 1E, 1F) within the device to, for example, stabilize or secure each of the microneedles **24, 124, 224** and/or provide for communication or fluidic coupling to fluid reservoir or compartment **132, 232**. Each of the microneedles **24, 124, 224** may have a length from the base **26, 126, 226** to free tip end **28, 128, 228** of 0.1 mm to 10 mm. For instance, the length from the base **26, 126, 226** to free tip end **28, 128, 228** may be 0.1-1, 0.1-2, 0.1-3, 0.1-4, 0.1-5, 0.1-6, 0.1-7, 0.1-8, 0.1-9, 0.1-10, 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 1-9, 1-10, 2-3, 2-4, 2-5, 2-6, 2-7, 2-8, 2-9, 2-10, 3-4, 3-5, 3-6, 3-7, 3-8, 3-9, 3-10, 4-5, 4-6, 4-7, 4-8, 4-9, 4-10, 5-6, 5-7, 5-8, 5-9, 5-10, 6-7, 6-8, 6-9, 6-10, 7-8, 7-9, 7-10, 8-9, 8-10, 9-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 mm. The plurality of microneedles **24, 124, 224** may all have the same length from the base **26, 126, 226** to the free tip end **28, 128, 228**. Alternatively, the plurality of microneedles **24, 124, 224** may have varying lengths relative to one another from the base **26, 126, 226** to the free tip end **28, 128, 228**. For example, one or more of the plurality of microneedles may have a different length (from the base to the free tip end) than one or more of the other of the plurality of microneedles. Such variation permits the device to, e.g., contour to the cortical plate of a subject. In addition, plurality of microneedles **24, 124, 224** may be regularly or irregularly spaced on first interior-facing surface **20, 120, 220** of head portion **18, 118, 218**. Plurality of microneedles **24, 124, 224** may be aligned in a plurality of regularly or irregularly spaced rows on first interior-facing surface **20, 120, 220** of head portion **18, 118, 218**. Each of said microneedles **24, 124, 224** may include a bore **30, 130, 230** (*see* Figures 1A and 1B). As will be readily appreciated, bore **30, 130, 230** is a hollow passage running the entire length of each of said plurality of microneedles **24, 124, 224**.

[0033] Plurality of microneedles **24, 124, 224** may be retractable within head portion **18, 118, 218** such that in a retracted position, each of the plurality of microneedles **24, 124, 224** is fully or partially contained in head portion **18, 118, 218**. The plurality of microneedles **24, 124, 224** may be actuated from an extended to a retracted position (and a retracted position to an extended position) using mechanical or electrical actuation mechanism. The exterior length from base **26, 126, 226** to free tip end **28, 128, 228** of plurality of microneedles **24, 124, 224** may also be adjusted in

this way, by actuating to a partially extended position using mechanical or electrical actuation mechanism.

[0034] With reference to Figures 1D-1F, 2A-2C, 3A, and 3B the cortical bone stimulation device **110, 210** according to the present invention may also be adapted to include a fluid reservoir or compartment **132, 232** suitable to retain a composition for delivery to a subject's tissue through the plurality of microneedles **124, 224**. For instance, the device **110, 210** according to the present invention may be used as described herein below to simultaneously deliver a composition **44** including, for example, exogenous growth factors to the area of application (i.e., are of tissue penetration) to take advantage of synergetic cortical bone stimulating effects of exogenous factors and endogenous factors. In this embodiment, fluid reservoir or compartment **132, 232** is in communication with bore **130, 230** of each of the plurality of microneedles **124, 224**. The communication between fluid reservoir or compartment **132, 232** and bore **130, 230** of each of the plurality of microneedles **124, 224** is such that a composition **44** contained within fluid reservoir or compartment **132, 232** may be expelled through bore **130, 230** of each of the plurality of microneedles **124, 224**, forming a fluidic pathway between fluid reservoir or compartment **132, 232** and bore **130, 230**. In this embodiment, the cortical bone stimulation device **110, 210** may also include a release mechanism **138, 238**, whereby actuation of the release mechanism releases contents of the fluid reservoir or compartment **132, 232** into the bore **130, 230** of and out the free tip end **128, 228** of each of the microneedles **124, 224**. The release mechanism can be any of those known in the art (e.g., those known for use with glucose testing devices (*see* U.S. Patent 9,463,463, which is hereby incorporated by reference in its entirety)) and may be manually, mechanically, or electronically actuated. In one embodiment, the exterior-facing surface **122, 222** of the head portion **118, 218** includes the release mechanism **138, 238**. In one embodiment, rest **134, 234** serves as the release mechanism **138, 238**, whereby manual pressure is applied to rest/release mechanism **134/138, 234/238** to force the contents of the fluid reservoir or compartment **132, 232** into the bore **130, 230** of and out the free tip end **128, 228** of each of the microneedles **124, 224**, as shown in Figures 2C, 3A, and 3B (arrows representing application of force or pressure to rest **134, 234**). Rest/release mechanism **134/138, 234/238** may be in the form of a push button or other type of button, operated by manual pressure,

mechanical trigger or switch, or electronical trigger or switch, or the like to inject the contents of the fluid reservoir or compartment **132, 232 into the subject's** tissue.

[0035] With reference to Figures 1F and 2A-2C, the device **210** may also include port or channel **236** in communication with fluid reservoir or compartment **232**. Port or channel **236** is adapted to receive, e.g., a tip of pipette **40** or needle **42** to facilitate filling or loading of device **210** with a composition. Also contemplated are embodiments like the one shown in Figures 1D, 1E, 3A, and 3B that do not include port or channel **236**. Such embodiments may be pre-filled or pre-loaded with a composition including, e.g., exogenous growth factors, during manufacture. Also contemplated are pre-filled inserts (e.g., disposable inserts) that head portion **118, 218** is adapted to receive. Such inserts would contain a composition to be delivered and fit within fluid reservoir or compartment **132, 232**.

[0036] Cortical bone stimulation device **10, 110, 210** may also include a removable cap affixed to interior-facing surface **20, 120, 220** of said head portion and covering the free-tip end **28, 128, 228** of each of the plurality of microneedles **24, 124, 224**.

[0037] The device **10, 110, 210** according to the present invention or portions thereof (e.g., head portion **18, 118, 218** or elongate handle **12, 112, 212**) may be fully disposable. For example, in one embodiment, the head portion **18, 118, 218** may be separable from the elongate handle **12, 112, 212** with the head portion **18, 118, 218** intended for single-use. The device **10, 110, 210** according to the present invention or portions thereof (e.g., head portion **18, 118, 218** or elongate handle **12, 112, 212**) may be also made of a material suitable for sterilization and reuse.

[0038] Another aspect of the present invention relates to a method for stimulation of cortical bone formation. The method involves providing a device according to the present invention, as described in detail above. The device includes an elongate handle having a proximal end and a distal end; a head portion extending from the proximal end of the elongate handle, the head portion having a first interior-facing surface and an opposing second exterior-facing surface; and a plurality of microneedles extending from, and perpendicular to, the first interior-facing surface of the head portion. Each of the plurality of microneedles has a base connected to the first interior-facing surface of the head portion and a free tip end. The method also involves positioning the free tip end of said plurality of microneedles in contact with

tissue of a subject, where cortical bone underlies the subject's tissue. The method further involves applying pressure to the device to cause the microneedles to penetrate the subject's tissue without penetrating the cortical bone underlying the subject's tissue, thereby stimulating formation of cortical bone underlying the subject's tissue.

[0039] In one embodiment, the subject's tissue is penetrated by the microneedles includes gingival tissue, periosteal tissue, or both. With reference to Figures 4A-4D, in one embodiment the cortical bone is craniofacial bone and the cortical bone stimulation device **10** according to the present invention is positioned relative to the area of interest having attached gingiva **A** and periosteum **B** with underlying cortical bone **C** (Figure 4A). Also shown is the trabeculae bone **D** that underlies cortical bone **C**. Pressure is applied to the device **10** in the direction of the large arrow shown in Figure 4B suitable to cause microneedles **24** to penetrate the subject's soft tissue without penetrating underlying cortical bone (Figures 4B and 4C) and the device **10** is then withdrawn (Figure 4D). This penetration of the soft tissue (i.e., attached gingiva **A** and periosteum **B**) without penetration of the underlying cortical bone **C** stimulates local release of endogenous growth factors under the periosteum (Figures 4C and 4D), which in turn stimulates new cortical bone growth **CC** (Figure 6).

[0040] As shown in Figure 4D, the method according to the present invention stimulates endogenous production of growth factors. Endogenous growth factors include (but are not limited to) osteogenic, osteoclastogenic, or angiogenic factors. *See, e.g.,* U.S. Patent No. 8,328,876 to Behnam et al., which is hereby incorporated by reference in its entirety. Such growth factors may include, but are not limited to, one or more insulin-like growth factors (IGF) (e.g., IGF-1 or IGF-2), platelet-derived growth factor (PDGF), fibroblast growth factors (FGF), vascular endothelial growth factor (VEGF), bone morphogenetic proteins (BMP) (e.g., BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7, BMP-8, BMP-9, BMP-10, BMP-11, BMP-12, and BMP-13), bone induction protein (BIP), transforming growth factors (TGF) (e.g., TGF-β), interleukins (e.g., IL-1β, IL-6, IL-8, IL-11, and IL-17), monocyte chemoattractant protein 1 (MCP-1 or CCL2), RANK ligand (RANKL), macrophage colony-stimulating factor (M-CSF), tumor necrosis factor alpha (TNFα), cathepsin K, or any other factor that stimulates or induces osteoclastogenesis or osteogenesis.

[0041] Although shown with respect to device **10** in Figures 4A-4D, it will be understood that the method according to the present invention may be carried out using any device described herein (including, e.g., device **110, 210** (*see*, e.g., Figure 5)). The method may involve use of the cortical bone stimulation device **110, 210** according to the present invention to deliver or inject a composition into the subject's tissue that has underlying cortical bone. For instance, in one embodiment, the method is carried out with a cortical bone stimulation device **110, 210** as shown in Figures 1D-1F, 2A-2C, 3A, 3B, and 5. The fluid reservoir **132, 232** may include a composition. The composition may include one or more exogenous growth factors. Suitable exogenous growth factors include (but are not limited to) osteogenic, osteoclastogenic, or angiogenic factors. *See, e.g.,* U.S. Patent No. 8,328,876 to Behnam et al., which is hereby incorporated by reference in its entirety. Such exogenous growth factors include, but are not limited to, one or more insulin-like growth factors (IGF) (e.g., IGF-1 or IGF-2), platelet-derived growth factor (PDGF), one or more Fibroblast Growth Factors (FGF), vascular endothelial growth factor (VEGF), bone morphogenetic proteins (BMP) (e.g., BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7, BMP-8, BMP-9, BMP-10, BMP-11, BMP-12, and BMP-13), bone induction protein (BIP), one or more transforming growth factors (TGF) (e.g., TGF-β), interleukins (e.g., IL-1β, IL-6, IL-8, IL-11, and IL-17), monocyte chemoattractant protein 1 (MCP-1 or CCL2), RANK ligand (RANKL), macrophage colony-stimulating factor (M-CSF), tumor necrosis factor alpha (TNFα), cathepsin K, or any other factor that stimulates or induces osteoclastogenesis or osteogenesis.

[0042] In one embodiment, the method involves use of a device having a head portion including an exterior port defining a passage in communication with the fluid reservoir. This method may also involve delivering a composition through the exterior port and into the fluid reservoir. For example, as shown in Figures 1F and 2A-2C, a composition including exogenous growth factors may be manually loaded into a fluid reservoir or compartment **232** within the device **210** (Figures 2A-2B) via exterior port (or channel) **236** suitable to receive a pipette tip **40** (shown), needle tip, or the like.

[0043] These embodiments facilitate injection of the composition (including, e.g., exogenous growth factors) to the area of interest by expelling the composition through bore **130, 230** of microneedles **124, 224** of the device **110**, **210** (Figures 2C,

3A, and 3B). In one embodiment, the method involves actuating a release mechanism as described above, whereby actuation of the release mechanism releases contents of the fluid reservoir or compartment **132, 232** into the bore **130, 230** and out the free tip end **128, 228** of each of the microneedles **124, 224**. In one embodiment, the exterior-facing surface **122, 222** of the head portion **118, 218** includes the release mechanism. In one embodiment, the exterior-facing surface **122, 222** of the head portion **118, 218** includes a rest **134, 234** adapted to receive a thumb or forefinger. The rest **134, 234** may be formed of an elastomeric material. In one embodiment, the rest **134, 234** serves as the release mechanism, whereby manual pressure is applied to rest/release mechanism **134/138, 234/238** to force the contents **44** of the fluid reservoir or compartment **132, 232** into the bore **130, 230** of and out the free tip end **128, 228** of each of the microneedles **124, 224**, as shown in Figures 2C, 3A, and 3B (arrows representing application of force or pressure to rest/release mechanism **134/138, 234/238**).

[0044] With reference to Figure 6, the method according to the present invention results in growth of newly formed cortical bone **CC** at the surface of the pre-existing cortical bone **C**. Although illustrated with respect to the dentofacial region, it will be appreciated that the method described herein may be used to stimulate cortical bone formation in other regions where cortical bone underlies soft tissue. For example, the methods and devices described herein may be used in any craniofacial region to cause cortical bone drift in a desired direction of soft tissue stimulation to, for example, restore bone shape in bone deficient or deformed areas. The methods described herein may also be used to drift cortical bone for cosmetic purpose to, e.g., improve facial aesthetics.

[0045] In one embodiment, the method according to the present invention is effective to induce osteogenesis or increase the rate of osteogenesis in cortical bone, as compared to when the method is not carried out. For example, Figures 7A and 7B are a schematic representations of changes in alveolar bone before expansion (Figure 7A) and after expansion (Figure 7B), illustrating of the effect of transverse orthodontic forces (F) on cortical bone in the absence of periosteal stimulation. Figures 8A and 8B are schematic illustrations of the effect of orthodontic force (F) and periosteal stimulation according to the method of the present invention (left panels of Figures 8A and 8B, small rectangles) in presence (Figure 8B) and absence

(Figure 8A) of exogenous growth factor (left panel of Figure 8B, teardrop shapes). Figure 8A illustrates the effect of periosteal stimulation according to the present invention that stimulates endogenous release of growth factors on the surface of the cortical bone as the tooth moves in response to orthodontic forces. Figure 8B illustrates the synergistic effect of periosteal stimulation according to the present invention that induces release of endogenous growth factors coupled with release of exogenous growth factors during application of orthodontic forces.

[0046] Accordingly, in one embodiment, the subject may be undergoing orthodontic treatment. For instance the subject may be undergoing treatment to effect tooth movement, jaw expansion, or correction of dentoalveolar discrepancies. In one embodiment, the subject has a defect in the cortical bone. The defect may be, for example, due to cleft palate, periodontal disease, or trauma.

[0047] Use of the method according to present invention may lessen the time the patient undergoes orthodontic treatment to move a tooth or expand a jaw from a first position to a second position, or to correct the dentoalveolar discrepancies, as compared to when the method is not carried out. The orthodontic treatment time may be lessened by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or more as compared to the length of time required to achieve the same result where the method is not carried out.

[0048] The method may also further include providing an orthodontic appliance on or near the tooth to be moved or jaw to be expanded to exert force on the tooth or jaw toward the desired position. The orthodontic appliance may be installed prior to and/or subsequent to carrying out the claimed method.

[0049] The subject may also be one that has received a graft, implant, prosthesis, or the like (e.g., bone graft, bone implant, bone prosthesis, or the like known in the art) that would benefit from enhanced bone integration within the body of the subject, as compared to when the method is not carried out. The graft may be from the patient (autograft), a donor (allograft), or artificial. Accordingly, the method may also further include providing and/or installing a graft, implant, or prosthesis within the area of bone stimulation according the method described herein to facilitate, e.g., integration of the graft, implant, or prosthesis. The graft, implant, or prothesis may be provided and/or installed prior to and/or subsequent to carrying out the claimed method. Use of the method according to present invention may lessen the

time for integration of the graft, implant, prosthesis, or the like, as compared to when the method is not carried out. The integration time may be lessened by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or more as compared to the length of time required to achieve the same result where the method is not carried out.

[0050] The methods described herein may also include first administering anesthesia to the subject. The methods described herein may also include first administering a local or topical anesthesia to the subject.

[0051] The subject may be any mammal. In one embodiment, the subject is a human. The subject may be an adult, child, or adolescent.

[0052] The methods of the present invention may be repeated as necessary to cause sufficient cortical bone growth, as a clinician determines necessary. For instance, the methods may repeated daily, one, two, three, four, five, six, seven, or more times per week, or one, two, three, four, five, eight, ten, twelve, fifteen, twenty or more times per month for a duration of, e.g., 1 to 12 months.

[0053] Another aspect of the present invention is directed to a kit for providing the components for carrying out stimulation of cortical bone formation, the kit including one or more of, a local anesthetic, a topical anesthetic, a syringe for application of local anesthetic, and a device (or detachable head portion thereof) according to the present invention as described herein in a disposable package.

EXAMPLES

Example 1 - Periosteal Stimulation Causes Cortical Bone Formation

[0054] As noted above, there is an enormous need for a technique that can stimulate bone formation at the surface of cortical bone, non-invasively to be able to expand the limit of orthodontic dental corrections.

[0055] To address this challenge, in the first series of experiments, rats (5 per group) were exposed to orthodontic transverse forces, applied to the upper molars and pushing towards the cortical bone (Figures 9A and 9B). After 56 days the animal were sacrificed and micro-CT images were collected. Figures 10A and 10B are micro-CT images of a control (no expansion) (Figure 10A) and expansion (Figure 10B) subjects collected after 56 days. In response to orthodontic forces, teeth were

moved towards the cortical bone (Figure 10B). As shown, the bone did not follow the tooth and, therefore, bone loss around the roots of the tooth was apparent (Figure 10B, top panel) and the cortical plate became thinner (Figure 10B, bottom panel).

[0056] In a second experimental group, in addition to transverse orthodontic forces, animals were exposed to periosteal stimulation around the area of first and second molar (arrows in Figure 11A and dots within the boxed area of Figure 11B) once per week. Periosteal stimulation was carried out with an appliance similar to the one depicted in Figure 12A-12C, with microneedles 3-5mm in length. After 56 days of expansion treatment these animals did not show any bone loss, and in addition cortical bone did not get thinner (Figures 13A and 13B). Fluorescent microscopy demonstrates significant increase in rate of bone formation in the area of cortical bone, that was clinically very significant, and never possible before (Figures 14A and 14B).

Example 2 - Periosteal Stimulation with Delivery of Exogenous Growth Factor Causes Synergistic Cortical Bone Formation

[0057] One possible reason for this stimulation may be the local release of growth factors in the area. Therefore, in another series of experiments, animals were divided into 3 groups: 1) control that did not receive any treatment; 2) animals that received injection of PDGF once per week (around first molar area); and 3) animals that received periosteal stimulation once per week in a similar area. No orthodontic force was applied to these animals/teeth. Compared to control (Figure 15A), the group that received injection of PDGF did not show significant bone formation (Figure 15B) while the group that received periosteal stimulation demonstrated significant bone formation (Figure 15C). These results indicate that the endogenous release of growth factors in response to periosteal stimulation is more effective to stimulate bone formation than injection of exogenous growth factors.

[0058] To see if this effect can accentuate the effect of bone remodeling that is stimulated by orthodontic forces, in another series of experiments, similar groups of animals were exposed to PDGF or periosteal stimulation in presence of orthodontic transverse forces. Fluorescent microscopy demonstrates that PDGF in presence of orthodontic forces was able to slightly increase the rate of bone formation, but this effect was very apparent in presence of periosteal stimulation (Figures 16A and 16B).

[0059] To evaluate if injection of exogenous growth factor can have synergic effects on endogenous release of growth factor, in another series of experiments, animals were weekly exposed to both periosteal stimulation and PDGF injection in presence of orthodontic forces. Fluorescent microscopy of these animals demonstrates significant increase in rate of bone formation in response to periosteal stimulation and demonstrates synergic effect between external and endogenous growth factors (Figure 16C).

[0060] Although preferred embodiments have been depicted and described in detail herein, it will be apparent to those skilled in the relevant art that various modifications, additions, substitutions, and the like can be made without departing from the spirit of the invention and these are therefore considered to be within the scope of the invention as defined in the claims which follow.

WHAT IS CLAIMED:

1. A device comprising:

an elongate handle having a proximal end and a distal end;

a head portion extending from the proximal end of said elongate handle, said head portion having a first interior-facing surface and an opposing second exterior-facing surface;

a plurality of microneedles extending from, and perpendicular to, the first interior-facing surface of said head portion, each of said plurality of microneedles having a base connected to the first interior-facing surface of said head portion and a free tip end.

2. The device according to claim 1, wherein the device is a dental device and said head portion is adapted for intra-**oral placement in a subject's mouth.**

3. The device according to claim 1 or claim 2, wherein each of said plurality of microneedles have the same length from the base to the free tip end.

4. The device according to claim 1 or claim 2, wherein one or more of said plurality of microneedles have varying lengths from the base to the free tip end.

5. The device according to any of claims 1-4, wherein each of said plurality of microneedles has a length from base to tip end of 0.1 mm to 10 mm.

6. The device according to any of claims 1-5, wherein said plurality of microneedles are aligned in a plurality of regularly spaced rows.

7. The device according to any of claims 1-5, wherein said plurality of microneedles are aligned in a plurality of irregularly spaced rows.

8. The device according to any of claims 1-7, wherein said plurality of microneedles are retractable within said head portion such that in a retracted position, each of said plurality of microneedles is fully contained in said head portion.

9. The device according to any of claims 1-8, wherein at least one of said plurality of microneedles comprises a bore.

10. The device according to claim 9, wherein said head portion further comprises a fluid reservoir in communication with the bore.

11. The device according to claim 10, wherein said head portion comprises an exterior port in communication with said fluid reservoir.

12. The device according to claim 10 or claim 11, wherein said head portion further comprises a release mechanism, whereby actuation of the release mechanism releases contents of the fluid reservoir through into the bore and out the tip end of each of said one or more microneedles comprising the bore.

13. The device according to claim 12, wherein the release mechanism is a manually-actuated release button.

14. The device according to claim 12, wherein the release mechanism is an electronically-actuated release button.

15. The device according to any of claims 1-14, wherein the exterior-facing surface of said head portion further comprises a rest adapted to receive a thumb or forefinger.

16. The device according to claim 15, wherein the rest is formed of an elastomeric material.

17. The device according to any of claims 1-16, wherein said head portion and said handle form a unitary structure.

18. The device according to any of claims 1-16, wherein said head portion is removably mounted to said handle.

19. The device according to any of claims 1-18, wherein the device further comprises:

a removable cap affixed to the interior-facing surfaceof said head portion and covering the free-tip end of said plurality of microneedles.

20. A method for stimulation of cortical bone formation, the method comprising:

providing a device comprising:

an elongate handle having a proximal end and a distal end;

a head portion extending from the proximal end of said elongate handle, the head portion having a first interior-facing surface and an opposing second exterior-facing surface;

a plurality of microneedles extending from, and perpendicular to, the first interior-facing surface of said head portion, each of said plurality of microneedles having a base connected to the first interior-facing surface of said head portion and a free tip end;

positioning the free tip end of said plurality of microneedles in contact with tissue of a subject, wherein cortical bone underlies the subject's tissue; and

applying pressure to the device to cause said microneedles to penetrate the subject's tissue without penetrating the cortical bone underlying the subject's tissue, thereby stimulating formation of cortical bone underlying the subject's tissue.

21. The method according to claim 20, wherein the device is a dental device and said head portion is adapted for intra-oral placement in a subject's mouth.

22. The method according to claim 21, wherein the subject's tissue comprises gingival tissue, periosteal tissue, or both.

23. The method according to any of claims 20-22, wherein the cortical bone is craniofacial cortical bone.

24. The method according to any of claims 20-23, wherein said plurality of microneedles have the same length from the base to the free tip end.

25. The method according to any of claims 20-23, wherein one or more of said plurality of microneedles have varying lengths from the base to the free tip end.

26. The method according to any of claims 20-25, wherein each of said plurality of microneedles has a length from base to tip end of 0.1 mm to 10 mm.

27. The method according to any of claims 20-26, wherein said plurality of microneedles are aligned in a plurality of regularly spaced rows.

28. The method according to any of claims 20-26, wherein said plurality of microneedles are aligned in a plurality of irregularly spaced rows.

29. The method according to any of claims 20-28, wherein said plurality of microneedles are retractable within said head portion such that in a retracted position, each of said plurality of microneedles is fully contained in said head portion.

30. The method according to any of claims 20-29, wherein at least one of said plurality of microneedles comprises a bore.

31. The method according to claim 30, wherein said head portion further comprises a fluid reservoir in communication with the bore.

32. The method according to claim 31, wherein the fluid reservoir comprises a composition.

33. The method according to claim 31, wherein said head portion comprises an exterior port defining a passage in communication with said fluid reservoir, and the method further comprises delivering a composition through the exterior port and into the fluid reservoir.

34. The method according to claim 32 or claim 33, wherein the composition comprises one or more osteogenic, angiogenic, and/or osteoclastogenic factors.

35. The method according to claim 34, wherein the one or more osteogenic, angiogenic, and/or osteoclastogenic factors comprise one or more insulin-like growth factors (IGF), platelet-derived growth factor (PDGF), fibroblast growth factors (FGF), vascular endothelial growth factor (VEGF), bone morphogenetic proteins (BMP), bone induction protein (BIP), transforming growth factors (TGF), interleukins, monocyte chemoattractant protein 1 (MCP-1 or CCL2), RANK ligand (RANKL), macrophage colony-stimulating factor (M-CSF), tumor necrosis factor alpha (TNFα), or cathepsin K.

36. The method according to any of claims 31-35, wherein said head portion further comprises a release mechanism, and wherein the method further comprises actuating the release mechanism and thereby releasing contents of the fluid reservoir into the bore and out the tip end of each of said one or more microneedles comprising the bore.

37. The method according to claim 36, wherein the release mechanism is a manually-actuated release button.

38. The method according to claim 36, wherein the release mechanism is an electronically-actuated release button.

39. The method according to any of claims 20-38, wherein said head portion and said handle form a unitary structure.

40. The method according to any of claims 20-38, wherein said head portion is removably mounted to said handle.

41. The method according to any of claims 20-40, wherein the device further comprises a removable cap affixed to the interior-facing surface of said head

portion and covering the free-tip end of said plurality of microneedles and wherein said method further comprises removing said removable cap prior to said positioning.

42. The method according to any of claims 20-41, wherein said applying is effective to increase endogenous production of one or more osteogenic, angiogenic, and/or osteoclastogenic factors in the subject's tissue compared to when the method is not carried out.

43. The method according to claim 42, wherein the one or more osteogenic, angiogenic, and/or osteoclastogenic factors comprise one or more of insulin-like growth factors (IGF), platelet-derived growth factor (PDGF), fibroblast growth factors (FGF), vascular endothelial growth factor (VEGF), bone morphogenetic proteins (BMP), bone induction protein (BIP), transforming growth factors (TGF), interleukins, monocyte chemoattractant protein 1 (MCP-1 or CCL2), RANK ligand (RANKL), macrophage colony-stimulating factor (M-CSF), tumor necrosis factor alpha (TNFα), or cathepsin K.

44. The method according to any of claims 20-43, wherein said applying is effective to induce or increase the rate of osteogenesis in cortical bone underlying the subject's tissue, as compared to when said applying is not carried out.

45. The method according to any of claims 20-44, wherein the method is carried out at least once per day, at least once per week, or at least once per month.

46. The method according to claim 45, wherein the method is carried out for 1 to 12 months.

47. The method according to any of claims 20-46 further comprising: administering local or topical anesthesia to the subject.

48. The method according to any of claims 20-47, wherein the subject is undergoing orthodontic treatment.

49. The method according to claim 48, wherein the subject is undergoing orthodontic treatment to effect tooth movement, jaw expansion, or correction of dentoalveolar discrepancies.

50. The method according to any of claims 20-49, wherein the subject has a defect in the cortical bone.

51. The method according to claim 50, wherein the defect is due to cleft palate, periodontal disease, or trauma.

52. The method according to any of claims 20-51, wherein the subject is a human.

53. The method according to claim 52, wherein the subject is an adult.

54. The method according to claim 52, wherein the subject is child or adolescent.

PERIOSTEAL STIMULATOR APPLIANCE FOR CLINICAL USAGE

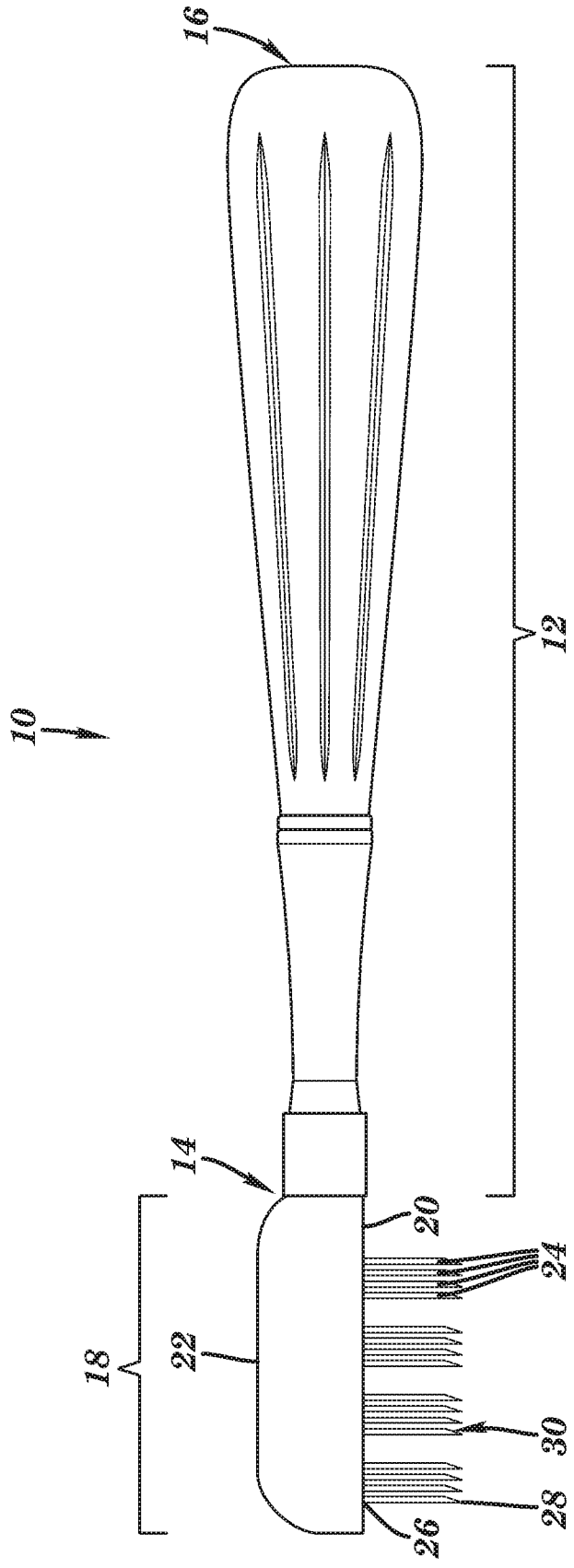

FIG. 1A

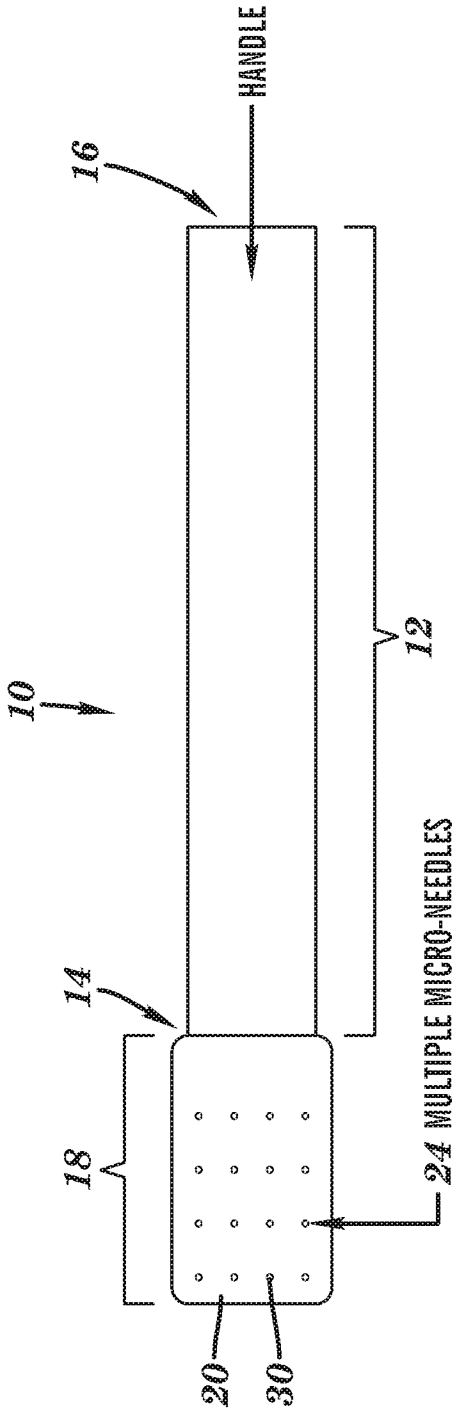
HANDLE
16
10
12
14
18
24 MULTIPLE MICRO-NEEDLES
20
30

FIG. 1B

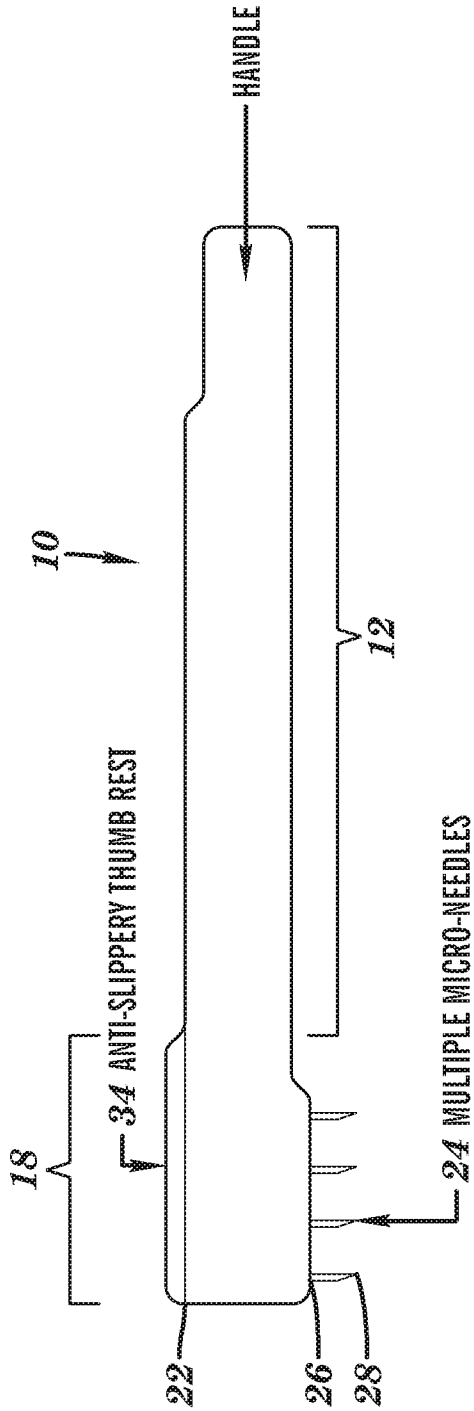
HANDLE
10
12
18
34 ANTI-SLIPPERY THUMB REST
24 MULTIPLE MICRO-NEEDLES
22
26
28

FIG. 1C

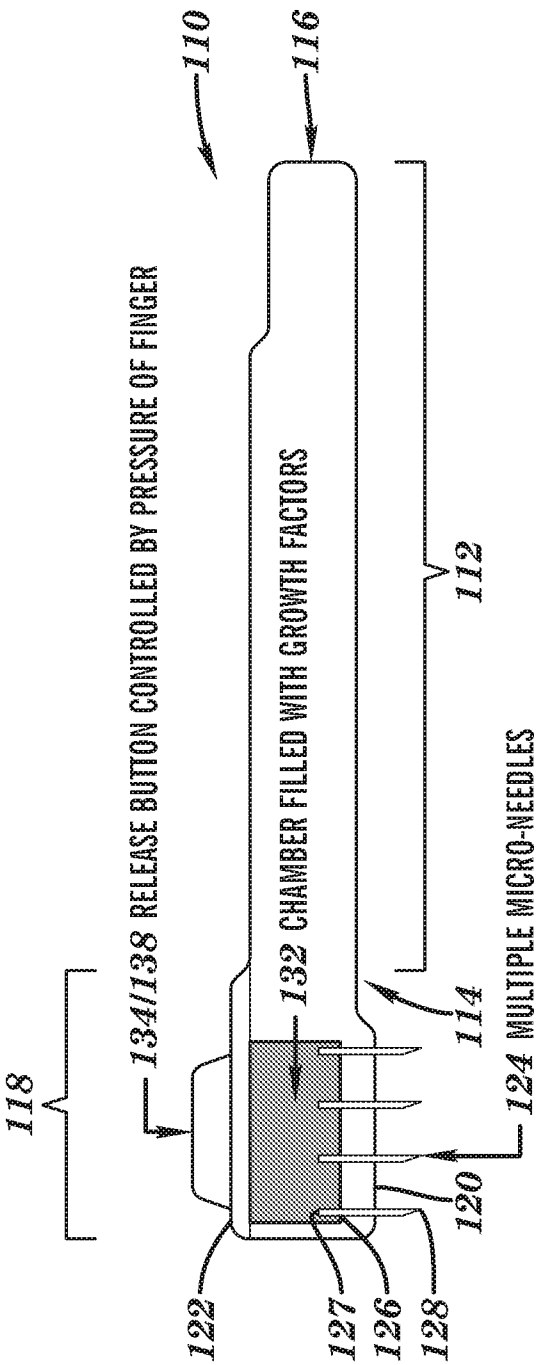
110
116
118
134/138 RELEASE BUTTON CONTROLLED BY PRESSURE OF FINGER
132 CHAMBER FILLED WITH GROWTH FACTORS
112
114
124 MULTIPLE MICRO-NEEDLES
120
122
127
126
128

FIG. 1D

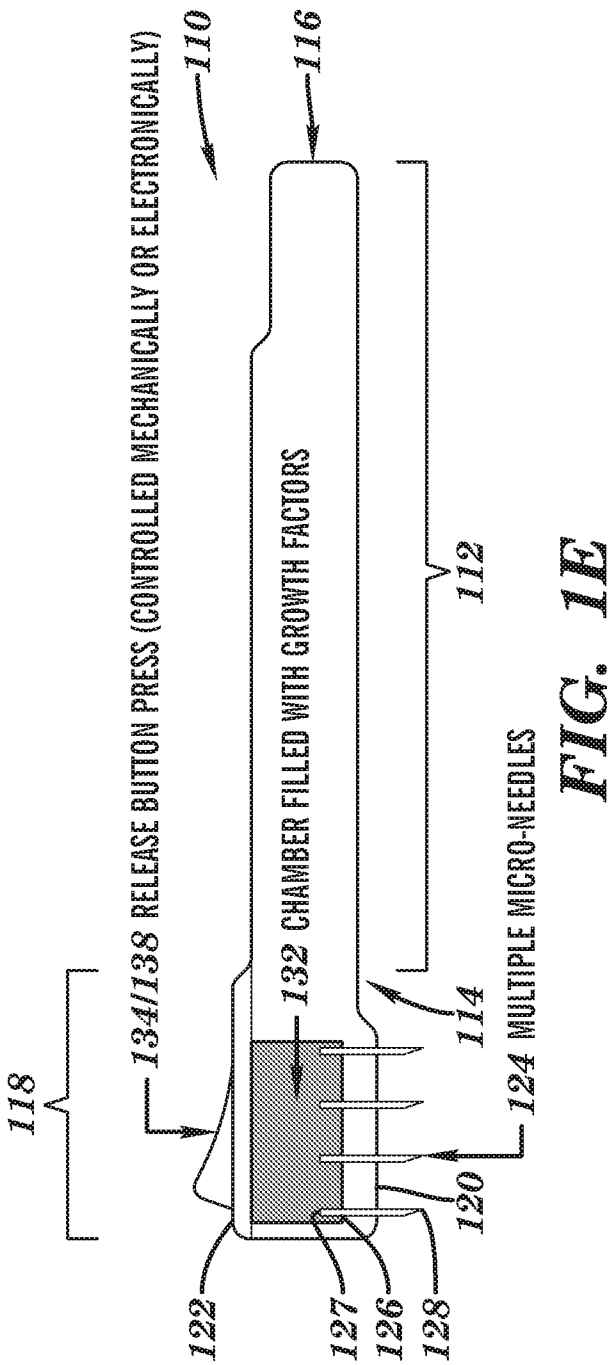
110
116
118
134/138 RELEASE BUTTON PRESS (CONTROLLED MECHANICALLY OR ELECTRONICALLY)
132 CHAMBER FILLED WITH GROWTH FACTORS
112
114
124 MULTIPLE MICRO-NEEDLES
120
122
127
126
128

FIG. 1E

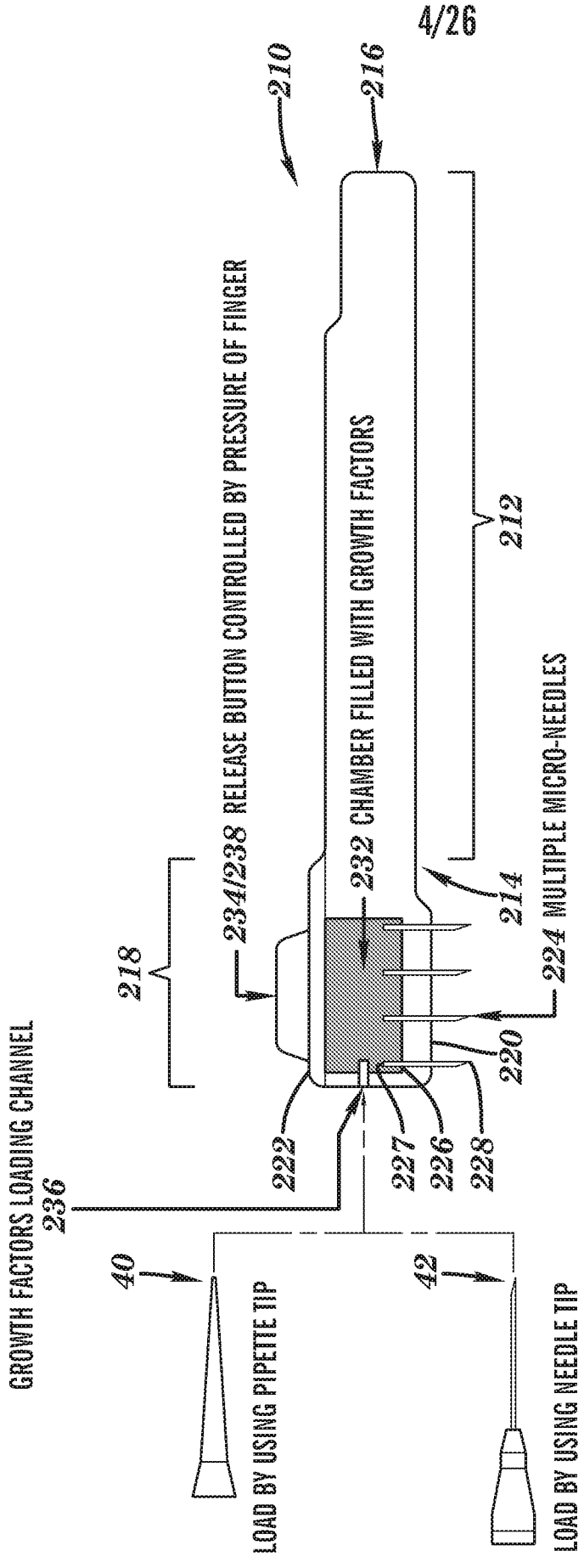
210
216
212
234/238 RELEASE BUTTON CONTROLLED BY PRESSURE OF FINGER
232 CHAMBER FILLED WITH GROWTH FACTORS
214
224 MULTIPLE MICRO-NEEDLES
218
220
222
227
226
228
GROWTH FACTORS LOADING CHANNEL
236
40
42
LOAD BY USING PIPETTE TIP
LOAD BY USING NEEDLE TIP

FIG. 1F

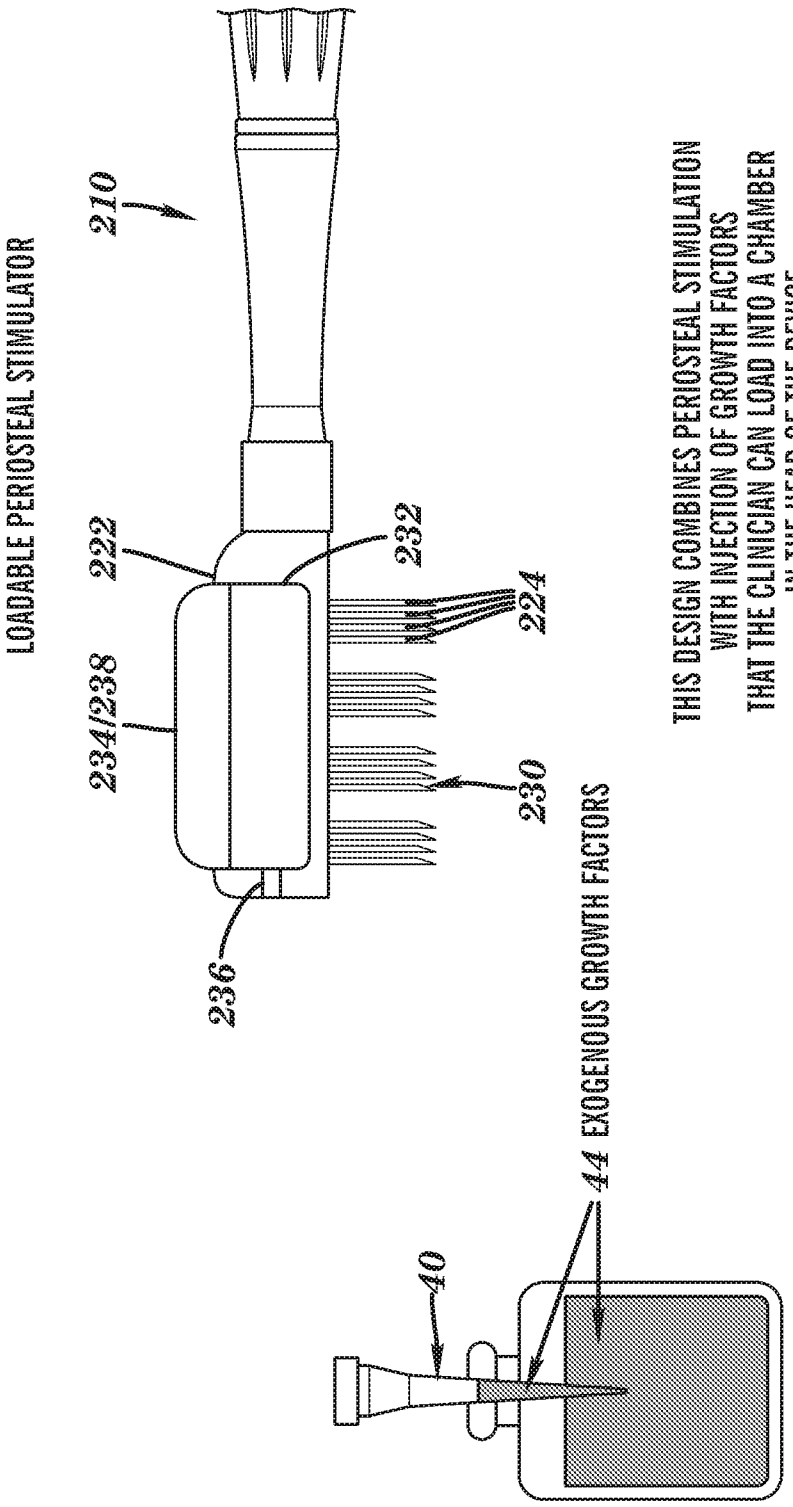
LOADABLE PERIOSTEAL STIMULATOR
210
222
232
224
234/238
230
236
44 EXOGENOUS GROWTH FACTORS
40
THIS DESIGN COMBINES PERIOSTEAL STIMULATION
WITH INJECTION OF GROWTH FACTORS
THAT THE CLINICIAN CAN LOAD INTO A CHAMBER
IN THE HEAD OF THE DEVICE

FIG. 2A

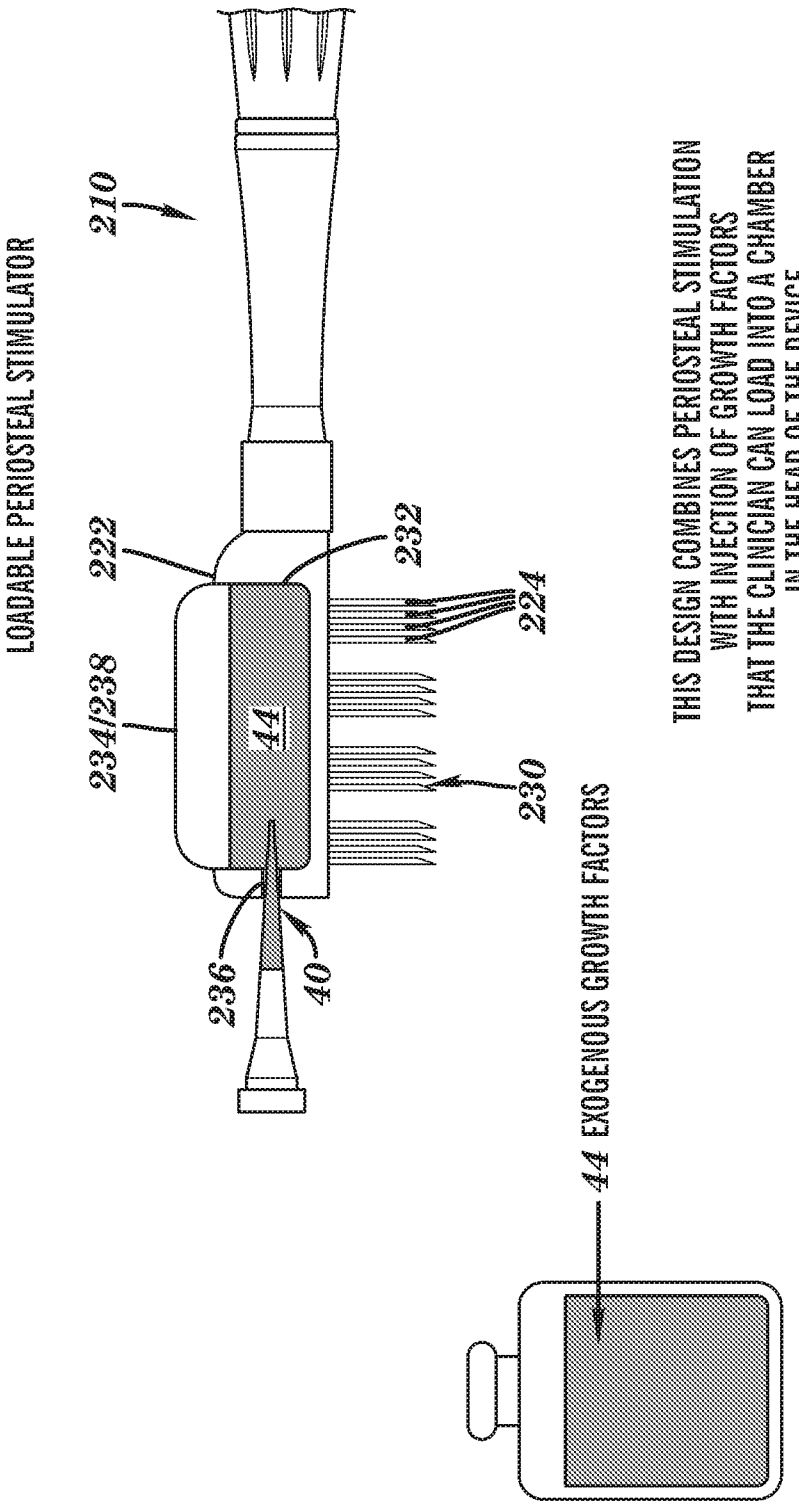
LOADABLE PERIOSTEAL STIMULATOR
210
222
232
224
234/238
44
230
236
40
44 EXOGENOUS GROWTH FACTORS
THIS DESIGN COMBINES PERIOSTEAL STIMULATION WITH INJECTION OF GROWTH FACTORS THAT THE CLINICIAN CAN LOAD INTO A CHAMBER IN THE HEAD OF THE DEVICE

FIG. 2B

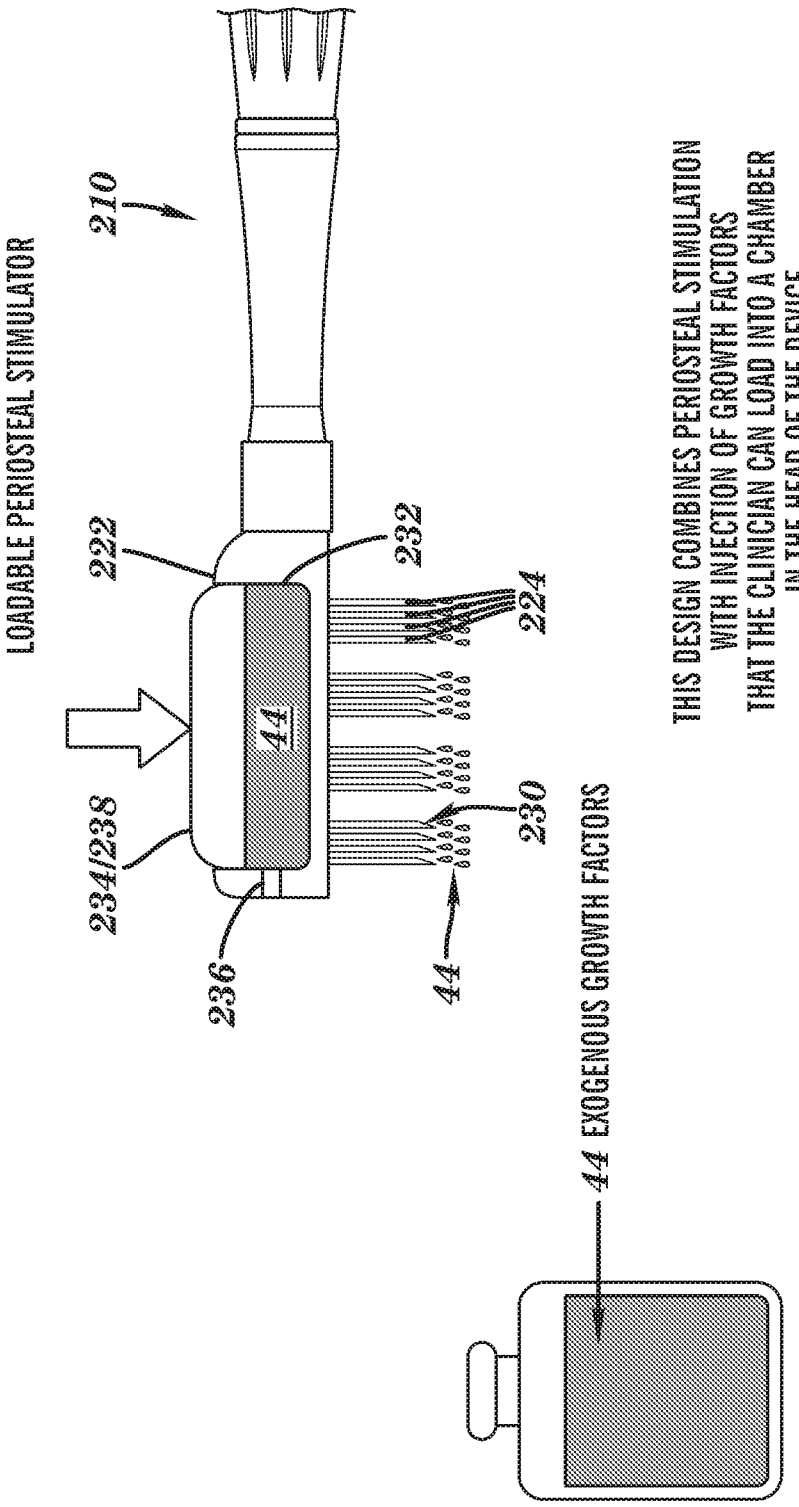
LOADABLE PERIOSTEAL STIMULATOR
210
222
232
224
44
234/238
230
236
44
44 EXOGENOUS GROWTH FACTORS
THIS DESIGN COMBINES PERIOSTEAL STIMULATION
WITH INJECTION OF GROWTH FACTORS
THAT THE CLINICIAN CAN LOAD INTO A CHAMBER
IN THE HEAD OF THE DEVICE

FIG. 2C

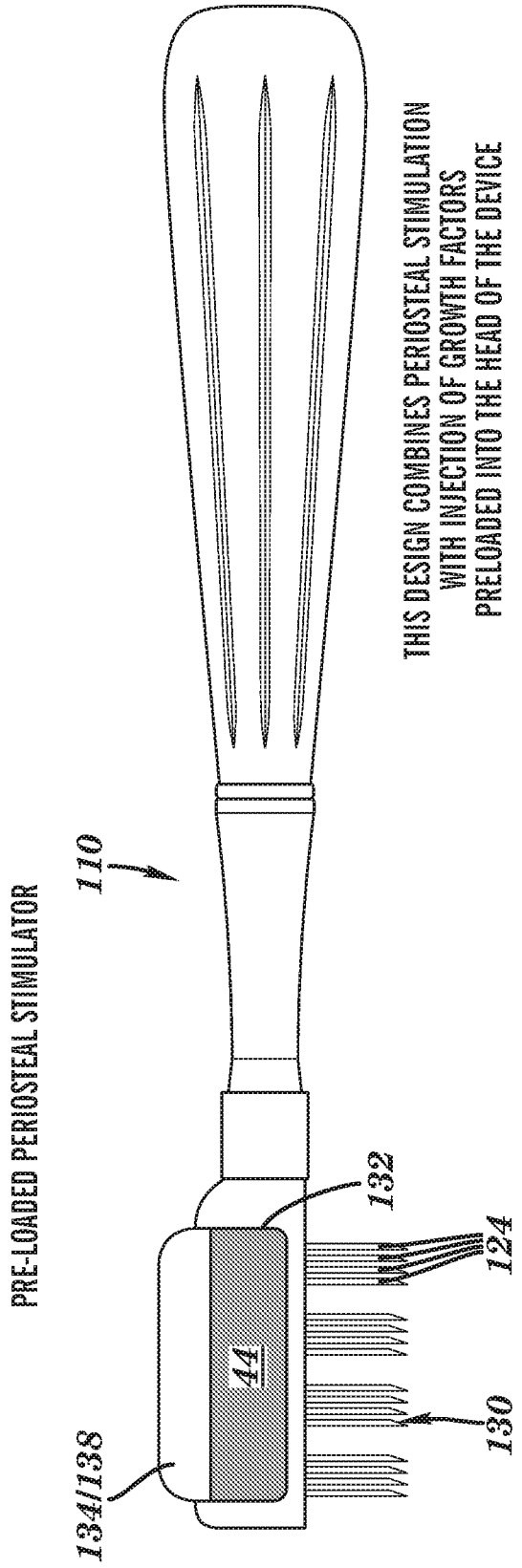
PRE-LOADED PERIOSTEAL STIMULATOR
110
132
124
44
130
134/138
THIS DESIGN COMBINES PERIOSTEAL STIMULATION
WITH INJECTION OF GROWTH FACTORS
PRELOADED INTO THE HEAD OF THE DEVICE

FIG. 3A

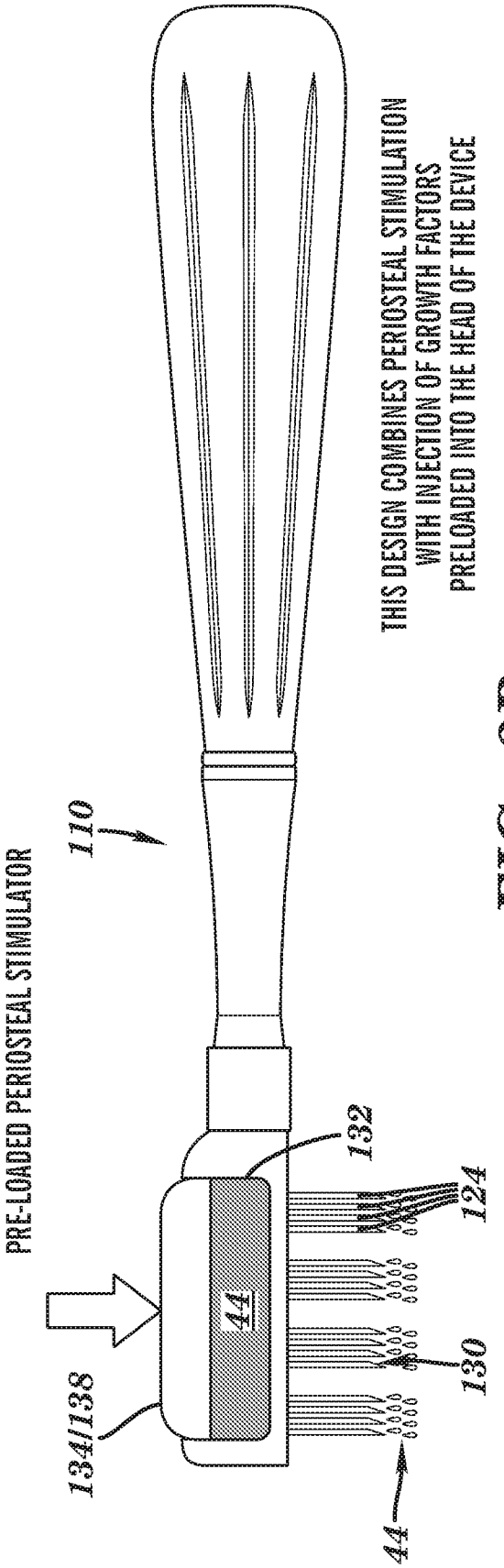
PRE-LOADED PERIOSTEAL STIMULATOR
110
132
124
44
130
134/138
44
THIS DESIGN COMBINES PERIOSTEAL STIMULATION
WITH INJECTION OF GROWTH FACTORS
PRELOADED INTO THE HEAD OF THE DEVICE

FIG. 3B

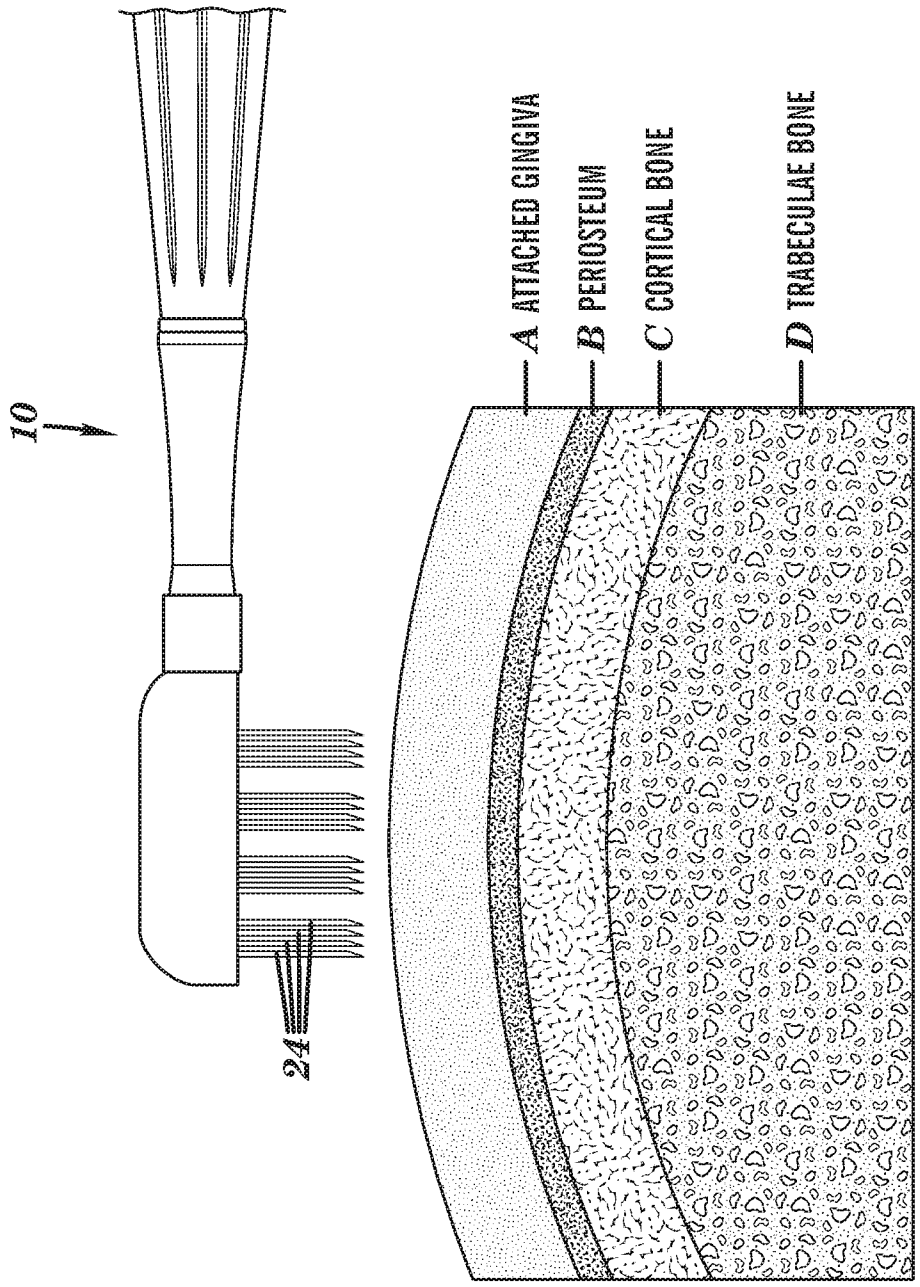
10
24
A ATTACHED GINGIVA
B PERIOSTEUM
C CORTICAL BONE
D TRABECULAE BONE

FIG. 4A

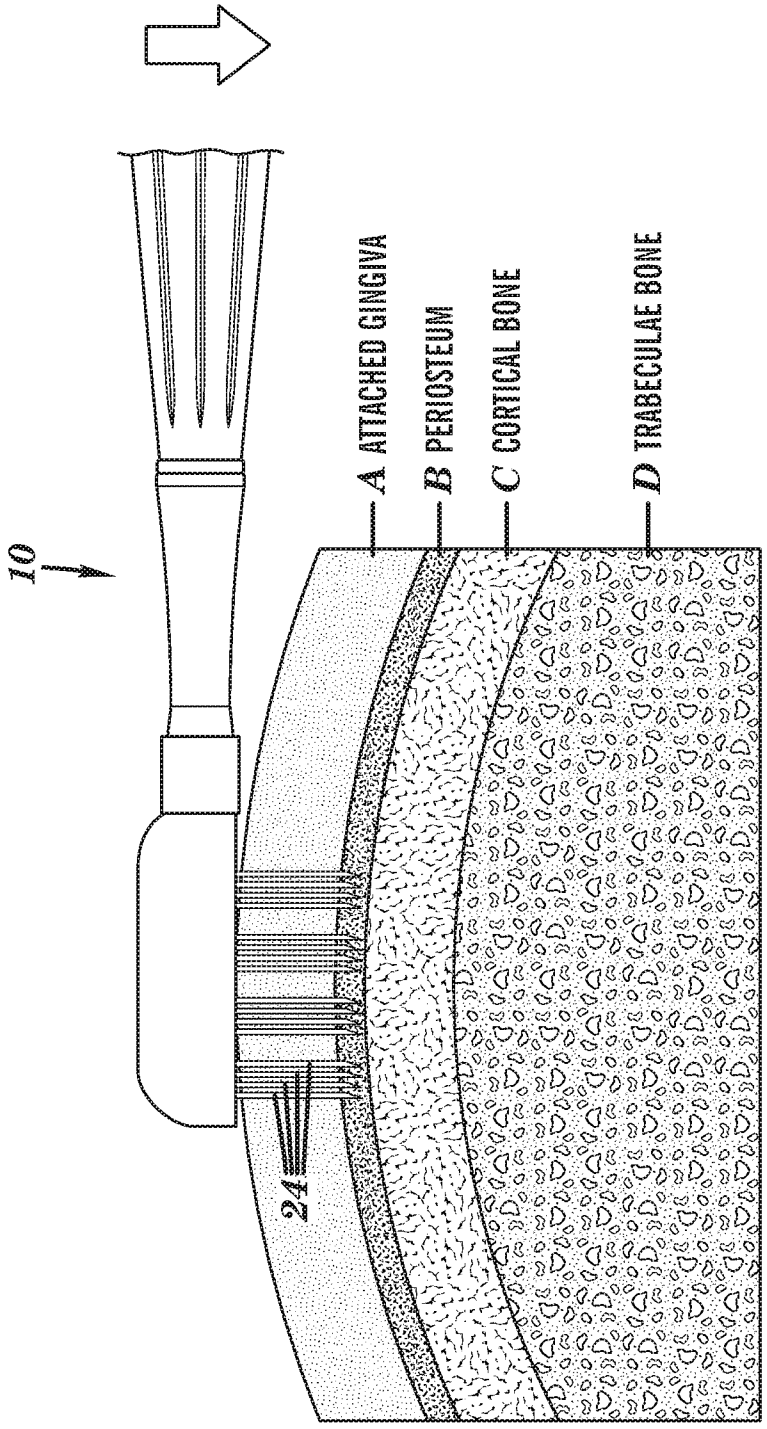
10
A ATTACHED GINGIVA
B PERIOSTEUM
C CORTICAL BONE
D TRABECULAE BONE
24

FIG. 4B

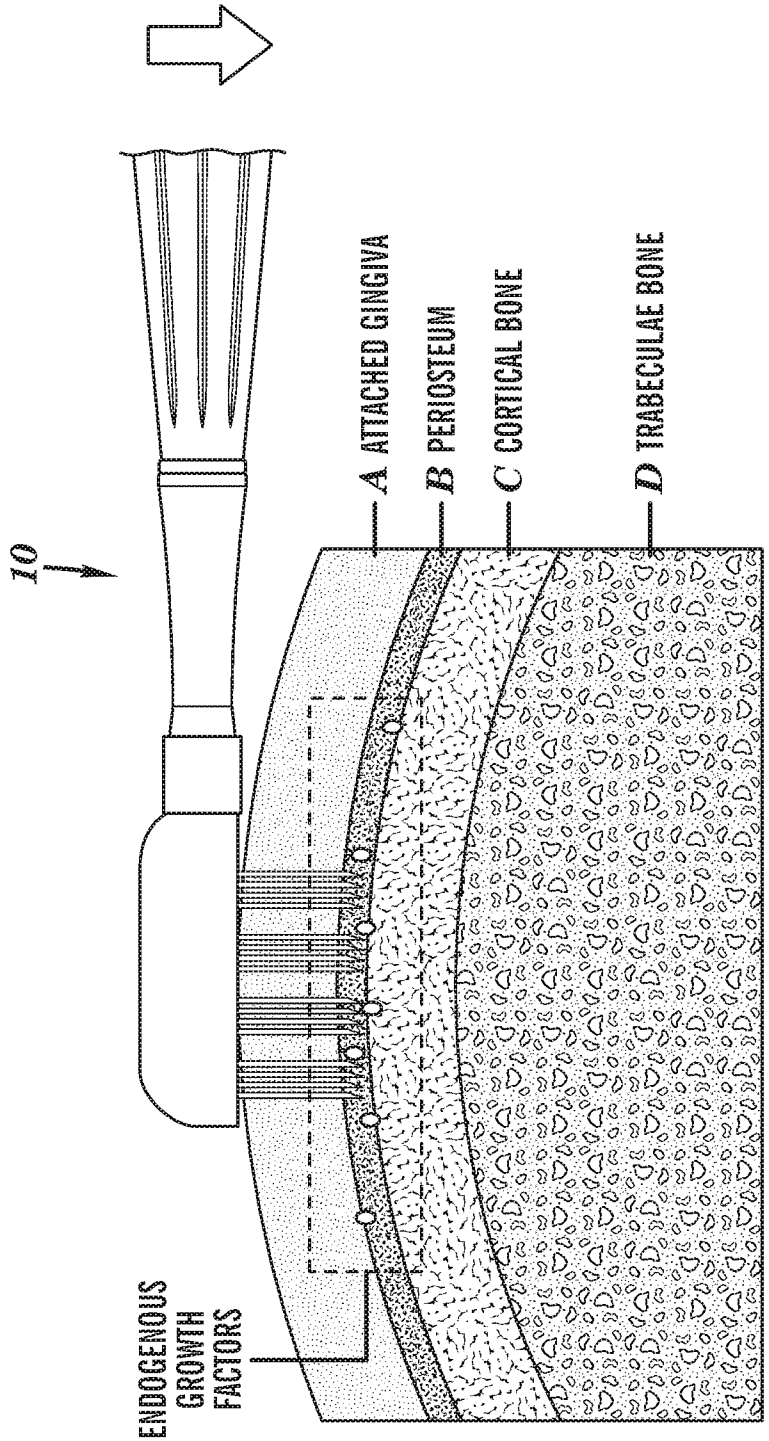
10
A ATTACHED GINGIVA
B PERIOSTEUM
C CORTICAL BONE
D TRABECULAE BONE
ENDOGENOUS GROWTH FACTORS

FIG. 4C

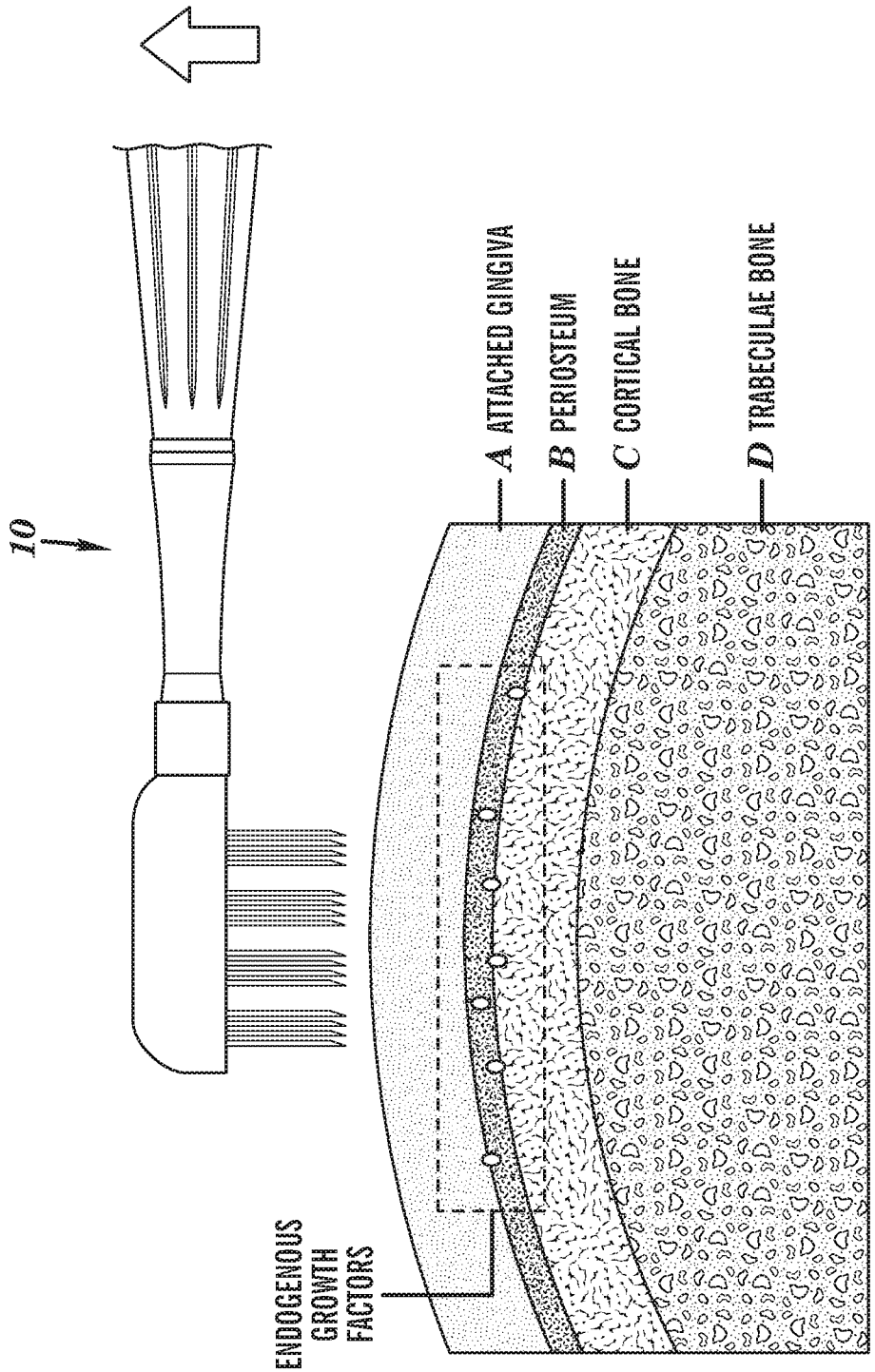
10
A ATTACHED GINGIVA
B PERIOSTEUM
C CORTICAL BONE
D TRABECULAE BONE
ENDOGENOUS GROWTH FACTORS

FIG. 4D

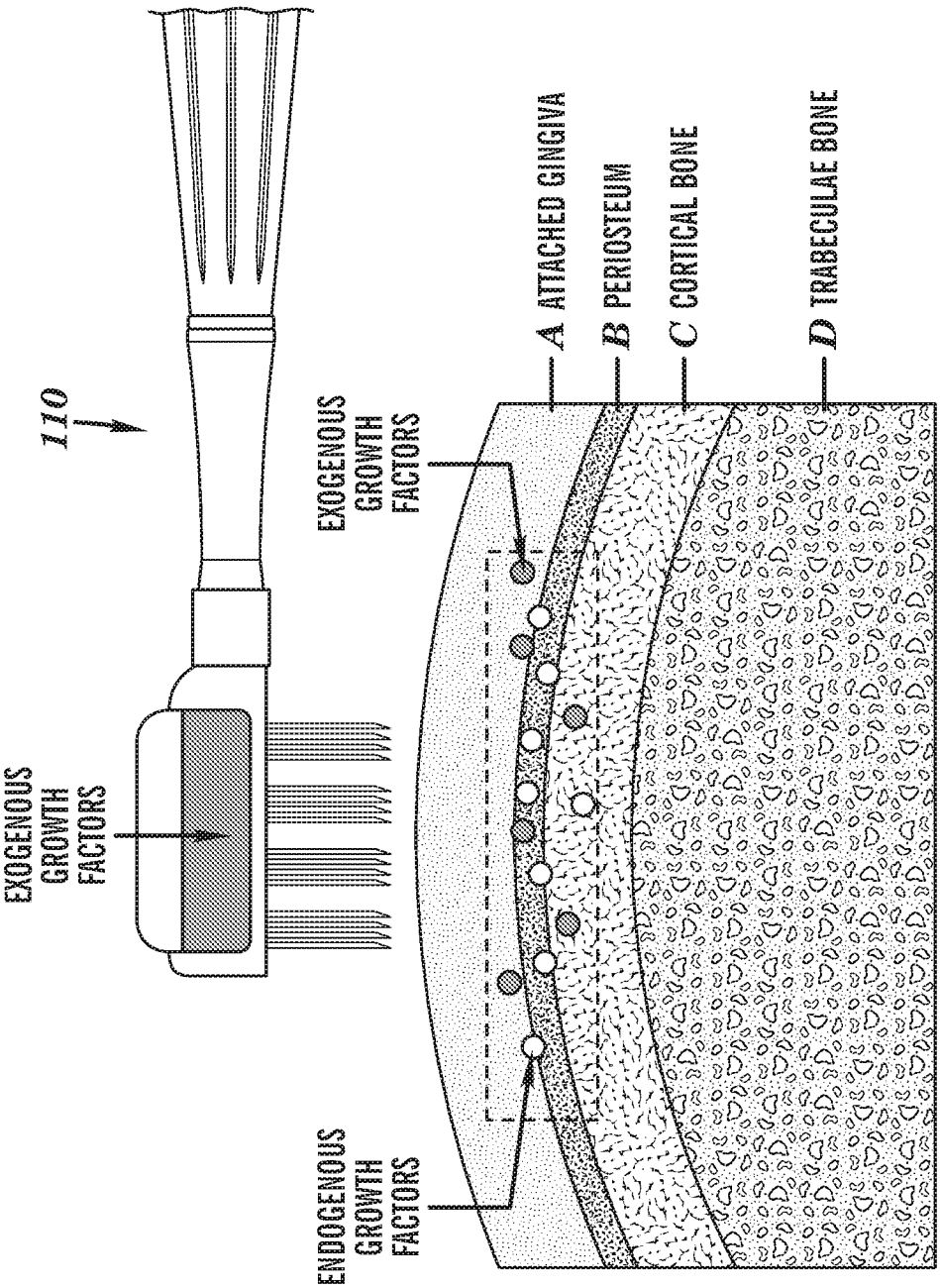
110
EXOGENOUS GROWTH FACTORS
EXOGENOUS GROWTH FACTORS
ENDOGENOUS GROWTH FACTORS
A ATTACHED GINGIVA
B PERIOSTEUM
C CORTICAL BONE
D TRABECULAE BONE

FIG. 5

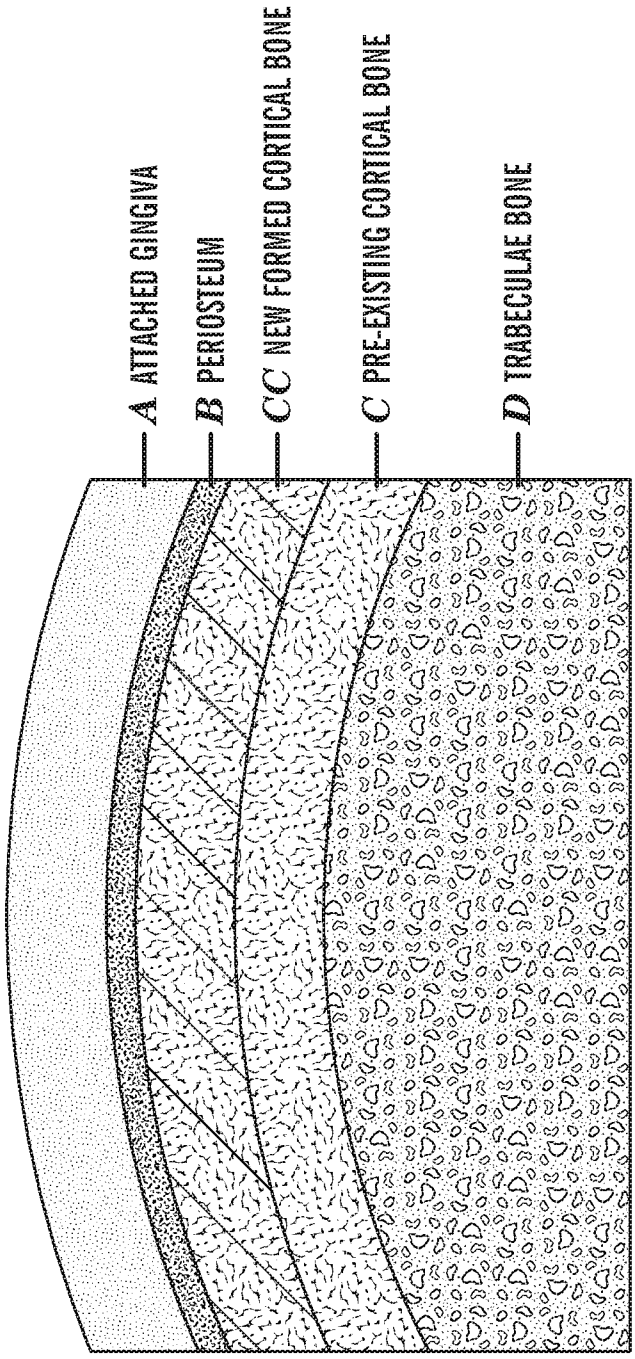
A ATTACHED GINGIVA
B PERIOSTEUM
CC NEW FORMED CORTICAL BONE
C PRE-EXISTING CORTICAL BONE
D TRABECULAE BONE

FIG. 6

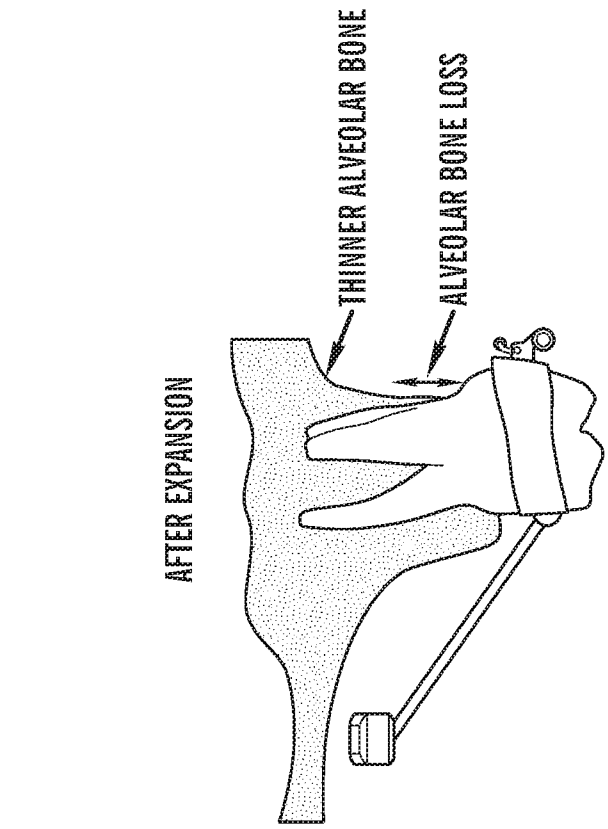

FIG. 7B

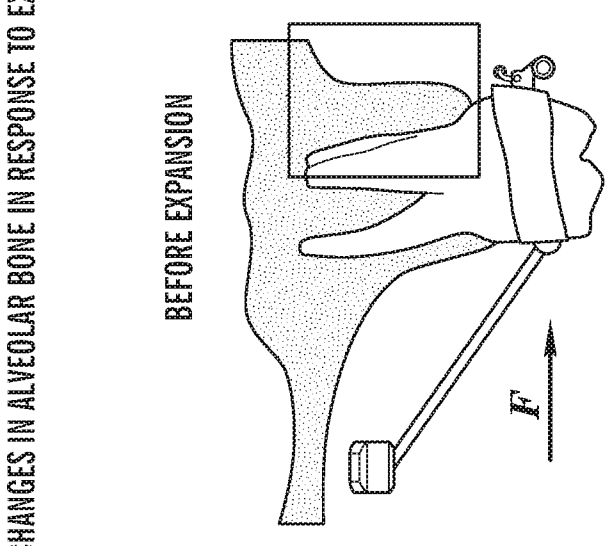

FIG. 7A

CHANGES IN ALVEOLAR BONE IN RESPONSE TO EXPANSION

ORTHODONTIC FORCE + PERIOSTEAL STIMULATION IN PRESENCE AND ABSENCE OF EXOGENOUS GROWTH FACTOR

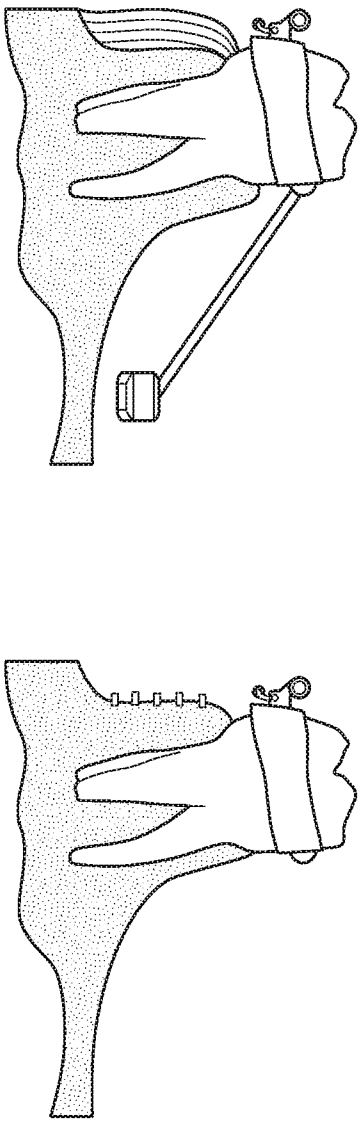

FIG. 8A

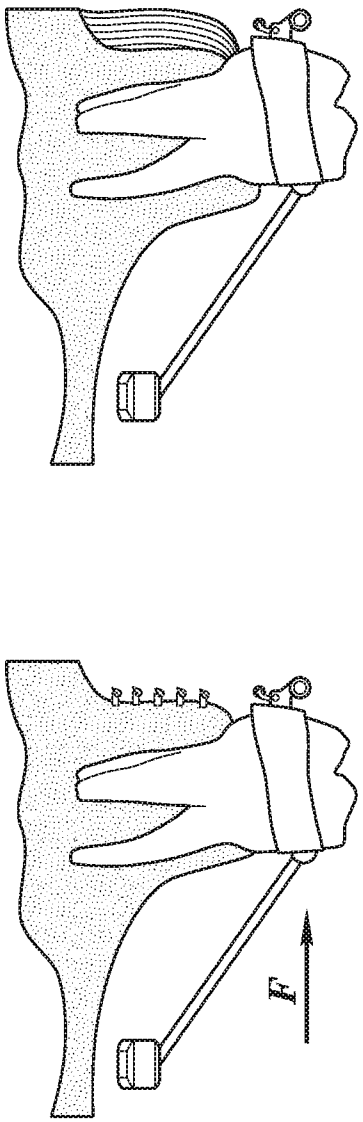

FIG. 8B

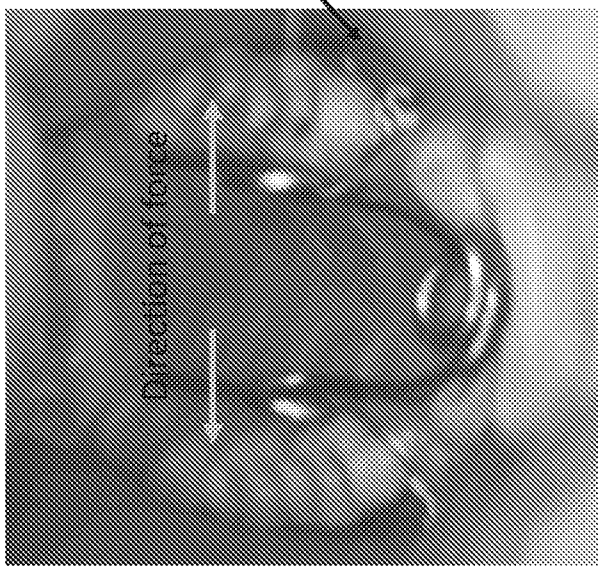
Application of Orthodontic Force
Direction of force
Cortical bone

FIG. 9A

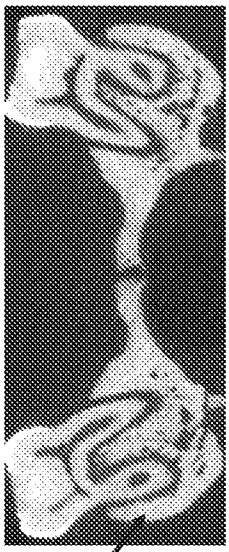

FIG. 9B

FIG. 10A

FIG. 10B

FIG. 11A

FIG. 11B

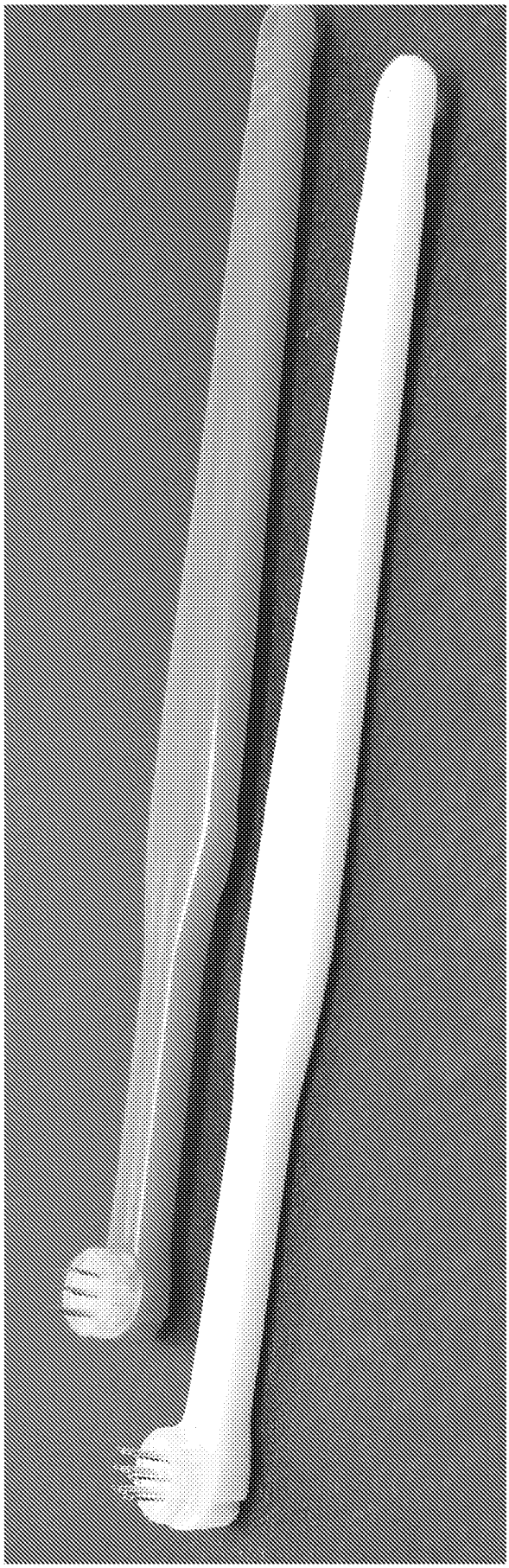

FIG. 12A

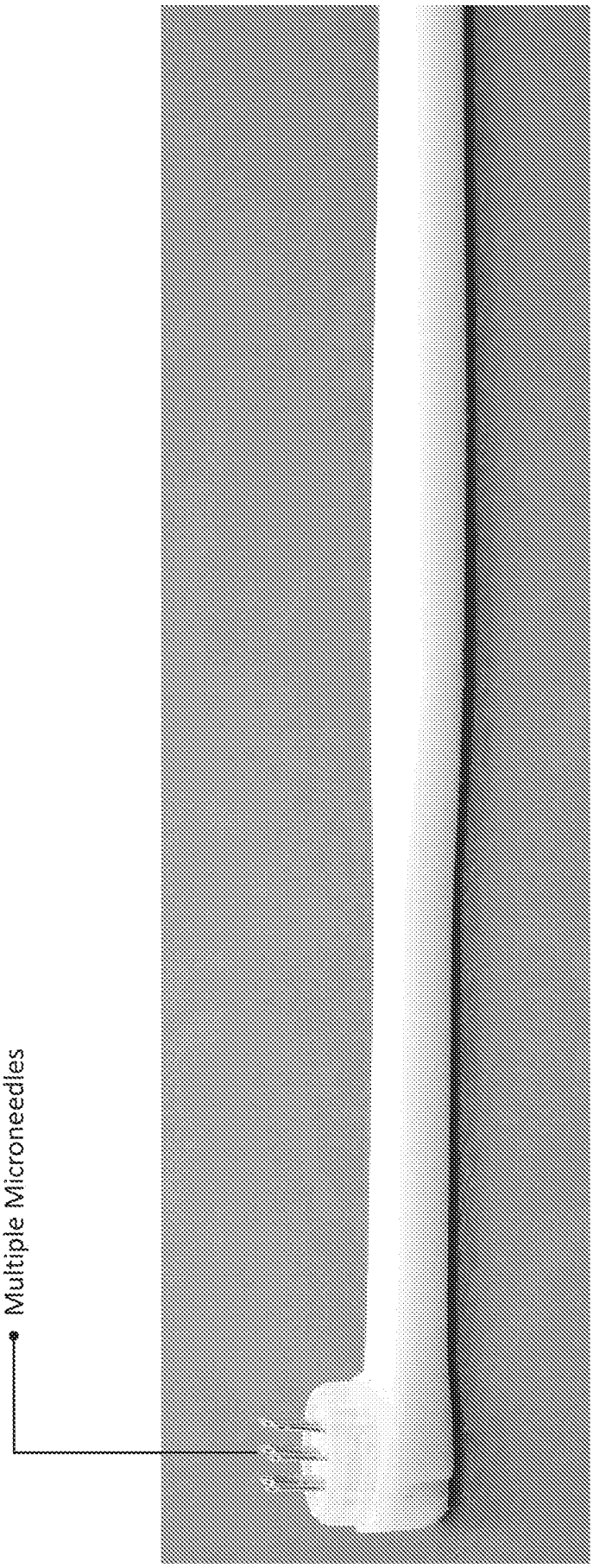

FIG. 12B

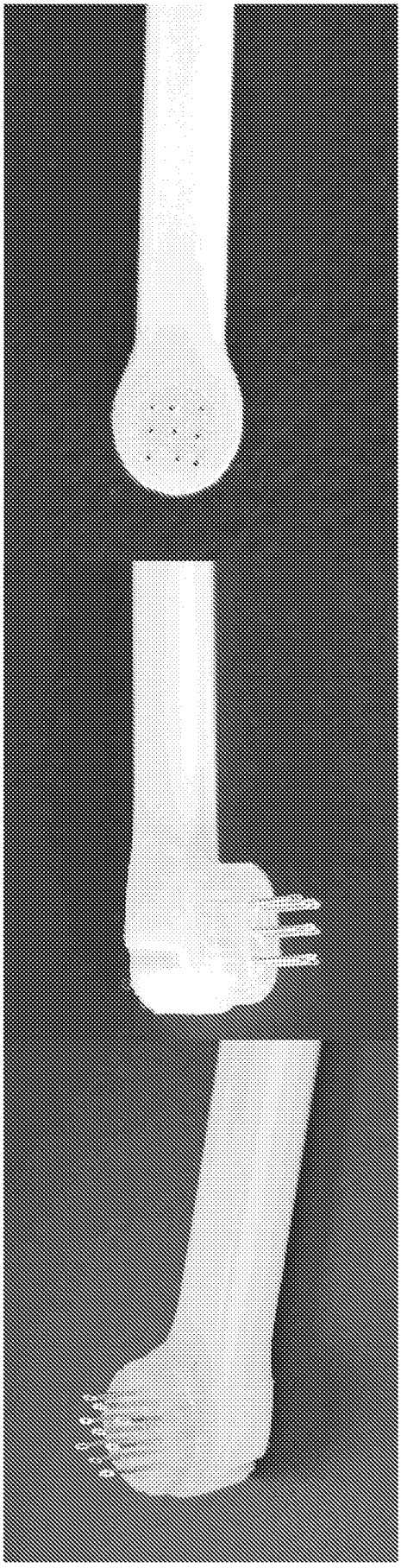

FIG. 12C

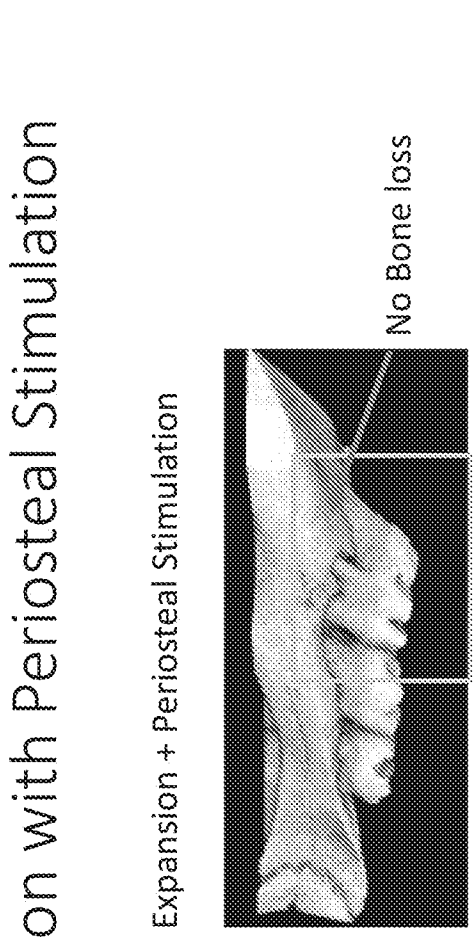

FIG. 13A

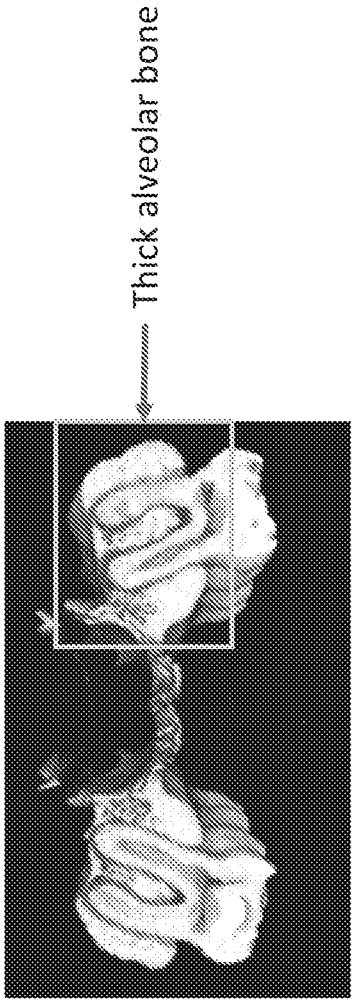

FIG. 13B

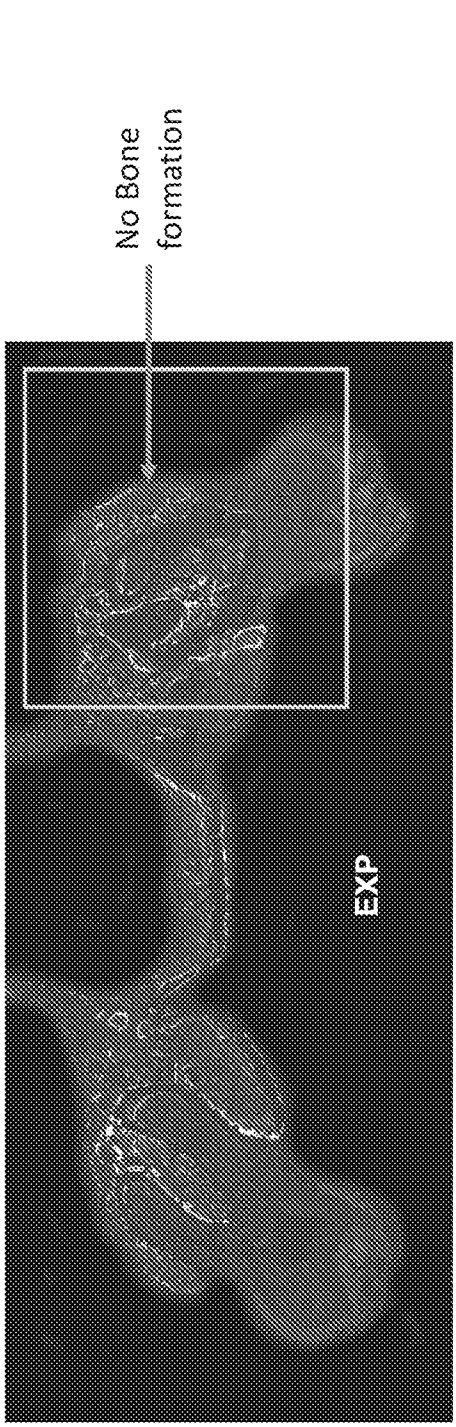

FIG. 14A

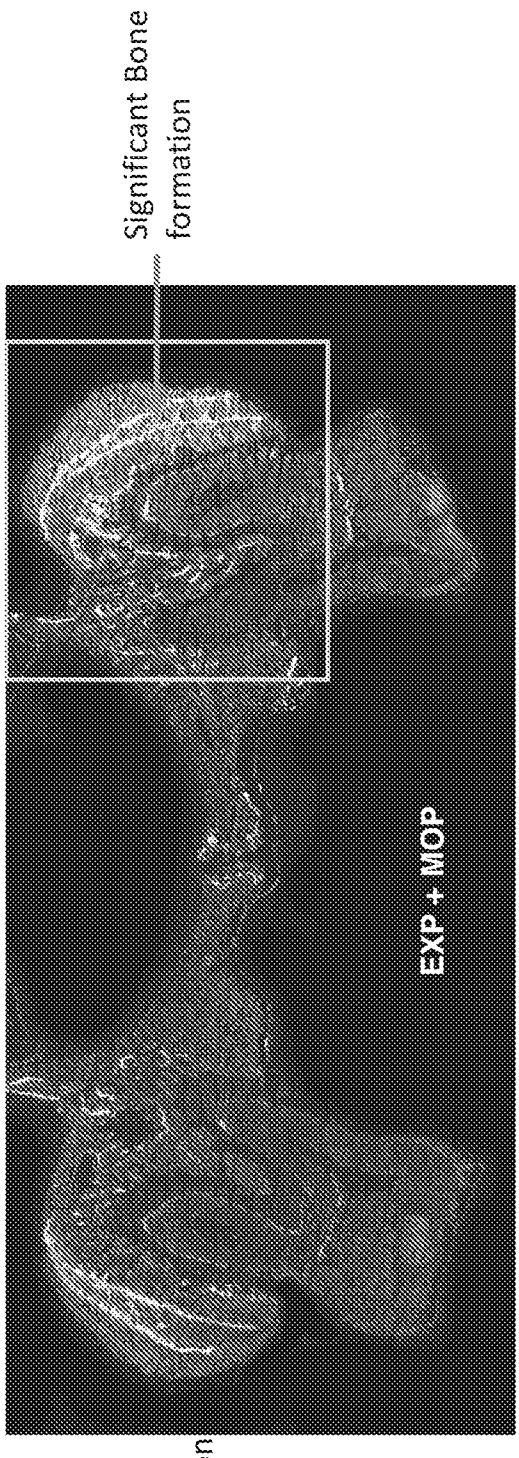

FIG. 14B

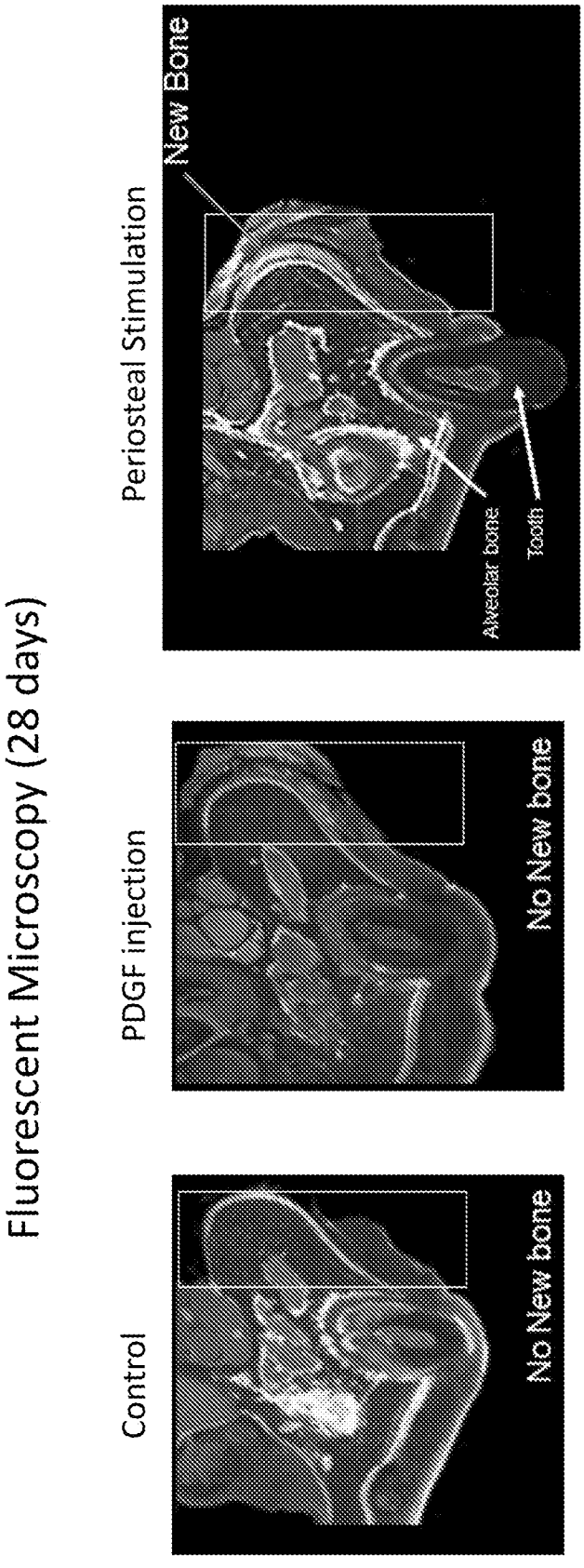

FIG. 15A

FIG. 15B

FIG. 15C

FIG. 16A

FIG. 16B

FIG. 16C

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 18/46900

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61M 37/00 (2018.01)
CPC - A61K 9/0021

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2014/012.1587 A1 (SALLBERG et al.); 01 May 2014 (01.05.2014); entire document, especially Figs. 22A-B, 23A-B, para. [0007], [0125], [0230]-[0232].	1-4
X -- Y	US 6,525,030 B1 (ERIKSSON); 25 February 2003 (25.02.2003); entire document, especially Fig. 1; col. 5, ln 28-59.	1, 3/1 ---------- 20-23
Y	US 2009/0053673 A1 (KLABUNDE et al.); 26 February 2009 (26.02.2009); entire document, especially para. [0010]-[0018].	20-23
A	US 2017/01733 16 A1 (3M INNOVATIVE PROPERTIES COMPANY); 22 June 2017 (22.06.2017); entire document.	1-4, 20-23
A	US 2015/0126923 A1 (UNIVERSITY OF PITTSBURGH OF THE COMMONWEALTH SYSTEM OF HIGHER EDUCATION); 07 May 2015 (07.05.2015); entire document.	1-4, 20-23
A	US 2015/0112250 A1 (THERAJECT INC); 23 April 2015 (23.04.2015); entire document.	1-4, 20-23

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 September 2018	19 OCT 2018

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 18/46900

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 5-19, 24-54
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.