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(54) Title: LIGAMENT REMODELING

(57) Abstract: A pharmaceutical composition comprising an active ingredient including a physiologically effective amount of a remodeling agent capable of altering properties of a Ligamentum Flavum (LF) so that the LF conforms to an available dimension of a spinal canal; and a pharmaceutically acceptable carrier, diluents and excipients.



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LIGAMENT REMODELING FIELD OF THE INVENTION

The present invention relates to spinal ligament remodeling, for example altering Ligamentum Flavum (LF) conformation.

5 BACKGROUND OF THE INVENTION

Spinal stenosis is generally defined as the narrowing of the spinal canal. Typically, pressure on the spinal cord and/or nerves is the result. Spinal stenosis can occur in a variety of ways in the spine. About 75% of cases of spinal stenosis occur in the low back (lumbar spine). Often, the sciatic nerve is affected.

10 Underlying causes:

Secondary changes associated with aging are the most common cause of stenosis. The ligaments of the spine can thicken with age. Alternatively or additionally, spurs may develop on the bones and project into the spinal canal. The cushioning disks between the vertebrae may begin to deteriorate. The facet joints also
15 may begin to thicken.

In some cases there is a genetic predisposition towards stenosis, for example if the spinal canal is too small at birth. Genetic predisposition may cause early onset stenosis.

Another potential cause of stenosis is abnormal growth of soft tissue. This can
20 affect the spinal canal directly by inflammation or by growth of tissue into the canal. Tissue growth may lead to bone resorption or displacement of bone and the eventual collapse of the supporting framework of the spinal column.

Symptoms

Common symptoms of stenosis include, but are not limited to, low back pain
25 and/or pain in the legs. Stenosis may pinch the nerves that control muscle power and sensation in the legs. Additional symptoms may include a foot-slapping gait, clumsiness, numbness, tingling, hot or cold feelings in the legs, weakness or a heavy and tired feeling in the legs. Patients may adopt a hunched or bent-over posture in order to alleviate these symptoms.

30 Diagnosis

Because of the general nature of the symptoms, spinal stenosis can be difficult to diagnose. Often, stenosis patients have no prior history of back problems or any discernible injury. Response to treatment may be a diagnostic indicator.

For example, relief of symptoms by postural changes and/or non-steroidal anti-inflammatory drugs may be indicative of onset of stenosis. In some cases, sophisticated spinal imaging (e.g. MRI or myelogram or CT) may be required to confirm the diagnosis. In some cases there is no apparent difference in medical
5 images from asymptomatic and symptomatic patients. In some cases a patient may exhibit marked clinical improvement with no apparent change in spine anatomy as assessed by imaging.

Available treatment options

Posture adjustment

10 People with spinal stenosis may find that flexing the spine by leaning forward while walking relieves their symptoms. Lying with the knees drawn up to the chest also can offer some relief. These positions enlarge the space available to the nerves and may make it easier for people with stenosis to walk longer distances. However, this hunched or bent posture may become a major symptom as the condition worsens.
15 In mild cases, rest followed by a gradual resumption of activity can relieve symptoms. Aerobic activity such as bicycling is often recommended. Alternatively or additionally, weight reduction can also relieve some of the load on the spine. A lumbar brace or corset may be employed to provide some support and can help the patient regain mobility. This approach is sometimes used with patients who have
20 weak abdominal muscles or older patients with degeneration at several levels of the spine. However, in cases where a patient bends the back to relieve pressure on a nerve, a brace which mandates an erect posture is of little value.

Systemic medications

In cases where pressure on the nerves is caused by and/or accompanied by
25 inflammatory swelling, nonsteroidal anti-inflammatory medications such as aspirin or ibuprofen may help relieve symptoms. These agents are typically administered systemically.

Local medication

In more severe cases, epidural steroid injections and/or calcitonin injections
30 may be employed to combat inflammation and/or regulate calcium uptake by bones. If this approach fails, surgical intervention may be required.

Acta Orthop Belg (1987) 53(3):409-11 and Acta Orthop Belg (1987) 53(2):170-72; each describe injection of Thiomucase in conjunction with an

anesthetic (Marcaine). The enzyme (Thiomucase) is used in place of cortisone. The articles conclude that "These products probably have a shrinking effect on the neural elements, creating more space for the blood vessels."

5 Cuckler et al. (1985; Journal of Bone & Joint Surgery - American Volume. 67(1):63-6) reported that they were unable to demonstrate clinical efficacy of injected steroids and cited reports by others of serious complications associated with this procedure.

10 US 6,806,251 teaches injection of a muscle paralyzing agent to spinal muscles as a method of pain relief. Botulism toxin (botox) is specifically described in this context.

Use of Calcitonin in the context of stenosis is described in "What you need to know about calcitonin injections"; The Cleveland Clinic Information Center [HTTP://www.clevelandclinic.org/health/health-info/docs/0600/0667](http://www.clevelandclinic.org/health/health-info/docs/0600/0667); and in "Calcitonin treatment in lumbar spinal stenosis; clinical observations" (1989) Calcif
15 Tissue Int. 45(6):372-74.

In 1992, Eskola et al. (Calcified Tissue International. 50(5):400-3) reported that Calcitonin therapy can be used as a conservative treatment in selected cases of lumbar spinal stenosis. Despite this report, calcitonin therapy is not widely used today.

20 US 6,736,835 teaches use of energy, including light energy to affect a variety of spinal targets including spinal ligaments.

Spinal Ligament composition

The Ligamentum Flavum (LF) has been studied in some detail, especially in the context of stenosis.

25 Yoshida et al. (1992; Spine 17(11): 1353-60) reported that the LF undergoes changes including proliferation of type II collagen, ossification and calcium crystal deposition. They stressed that Type II collagen proliferates from the enthesis to the ligament side.

Specchia et al. (2001; J Orthop Res.: 19(2):294-300) reported that LF cells
30 from stenotic patients contain osteonectin, type II and type X collagen as well as S100 protein. LF from control patients lacked these components.

Chen et al. (2000; Anal Biochem. 278(2):99-105) reported that Pentosidine (Pen) which is a senescent crosslink representing an advanced glycation end product

accumulates in tissue proteins including collagen. The correlation between Pen levels and age was significant.

Okada et al. (1993) concluded that high molecular weight proteoglycans become more prevalent in human LF as age increase. The high molecular weight
5 proteoglycans consisted mainly of chondroitin 6-sulfate.

In a study on rabbit Lf, Nihei et al. (2003; Anatomical Science International; 78(3):162) concluded that the LF in lower thoracic and lumbar regions is enriched in elastic fibers.

With respect to the spinal dura mater (DM), Nakagawa et al. (Spine (1994)
10 19(19):2164-9) concluded that the DM contains more elastin on its dorsal side than on its ventral side.

These publications and/or patent specifications are fully incorporated herein by reference to the same extent as if each had been individually incorporated herein by reference.

15 US patent application 2005/0084801 by EliHafidi et al., the disclosure of which is fully incorporated herein by reference, teaches hydrolysis to convert collagen into a water soluble polypeptide using alkaline or acid reagents. During hydrolysis denaturation occurs and the helical structure of the collagen is disrupted. Conditions such as the concentration of the acid or alkaline, the specific acids or alkalines used
20 for the hydrolysis, the temperature of the hydrolysis and the duration of the hydrolysis can be adjusted to produce a polypeptide product which is water soluble and has a desired average molecular weight.

The use of collagenase *in vivo* for digestion of ligaments in the hand has been reported in the context of Dupuytren's disease (e.g. Hurst and Badalamente (1999)
25 Hand Clin. 1591):97-107 vii; Hurst and Badalamente (2000) J Hand Surg[Am] 25(4):629-636; Starkweather et al. (1996) J Hand Surg [Am] 21(3):490-495; Badalamente et al. (2002) J Hand Surg[Am] 27(5):788-798; each of these references is fully incorporated herein by reference). The treatment is considered safe and effective and may alleviate symptoms for two to three years (D.M. McCarthy (1992) J
30 Hand Surg [Br]17(3):356; fully incorporated herein by reference)

Surgical intervention

Accepted surgical treatment typically involves laminectomy and ligament resection and/or lumbar fusion. Ligament resection and/or lumbar fusion may serve to supplement the laminectomy.

5 A less established surgical option (Dynesys) involves fusionless instrumentation.

SUMMARY OF THE INVENTION

10 An aspect of some embodiments of the present invention relates to a method of spinal ligament remodeling. In an exemplary embodiment of the invention, ligament remodeling relieves symptoms of spinal stenosis by relieving pressure on an adjacent nerve. In an exemplary embodiment of the invention, pressure is relieved because the remodeled ligament is softened and/or reduced in size and/or partially dissolved. Optionally, remodeling permits the ligament to conform to available space
15 in the spinal canal. These changes may optionally alter ligament thickness and/or shape. In an exemplary embodiment of the invention, the Ligamentum Flavum (LF) is the target of remodeling. In an exemplary embodiment of the invention, the change in conformation results from a change in a ligament component as opposed to a reduction in an inflammatory response. Optionally, the change in the ligament
20 component may be a chemical and/or a physical change.

 In an exemplary embodiment of the invention, remodeling is by direct application of a remodeling agent to the ligament. Application may be, for example, by injection. Optionally, the dura mater (DM) is not significantly affected by the injection. In an exemplary embodiment of the invention, remodeling is of a facet
25 capsule instead of, or in addition to, the LF.

 In an exemplary embodiment of the invention, remodeling causes a small change in a crucial ligament dimension and/or physical property which produces a significant clinical difference. Optionally, images of spine from an ambulatory post remodeling patient and the same patient debilitated by stenosis prior to remodeling do
30 not indicate an apparent difference. Optionally, a small, but clinically significant difference in ligament conformation is apparent in CT scans or MRI images.

 An aspect of some embodiments of the present invention relates to use of a remodeling agent capable of altering properties of a ligament. In an exemplary

embodiment of the invention, the remodeling agent acts specifically on a target ligament without significant effect on adjacent tissue. In an exemplary embodiment of the invention, specificity of the remodeling agent is achieved by direct application to a target ligament. Optionally, the agent is a chemical, optionally an enzyme. Optionally,
5 the agent works preferentially on the LF in comparison to other tissues, for example the dura mater. In an exemplary embodiment of the invention, the remodeling agent is provided as a pharmaceutical composition and/or an article of manufacture including instructions for use in ligament remodeling.

An aspect of some embodiments of the present invention relates to applying
10 energy to a spinal ligament to alter properties of the ligament so that the ligament is remodeled. Optionally, the energy is applied to the ligament via a probe inserted into the body. In an exemplary embodiment of the invention, an energy delivery apparatus configured to deliver energy to a spinal ligament is provided.

In an exemplary embodiment of the invention, there is provided a
15 pharmaceutical composition, the pharmaceutical composition comprising:

(a) an active ingredient including a physiologically effective amount of a remodeling agent capable of altering properties of a Ligamentum Flavum (LF) so that the LF conforms to an available dimension of a spinal canal; and

(b) a pharmaceutically acceptable carrier, diluents and excipients.

20 Optionally, the pharmaceutical composition is supplied as an article of manufacture additionally comprising:

(c) packaging material and

(d) instructions for use in remodeling of the LF.

Optionally, the article of manufacture is supplied as a unit dosage form.

25 Optionally, the unit dosage form includes at least a portion of a tool for locally applying said remodeling agent to said LF.

Optionally, the remodeling agent includes at least one chemical capable of locally adjusting a pH of at least a portion of the LF.

Optionally, the remodeling agent includes an enzyme.

30 Optionally, the enzyme digests a substrate in the LF.

Optionally, the enzyme has negligible effect on substrates found in the dura mater.

Optionally, the alteration of properties refers to softening.

Optionally, the alteration of properties refers to partial dissolution.

In an exemplary embodiment of the invention, there is provided a method of ligament remodeling, the method comprising:

- (a) applying a ligament remodeling agent to a ligament;
- 5 (b) causing the ligament to conform to an available space.

Optionally, the method is applied to a spinal ligament in a spinal canal.

Optionally, the spinal ligament includes a Ligamentum Flavum (LF).

Optionally, the applying is directly to said ligament.

Optionally, the applying is by injection into said ligament.

- 10 Optionally, causing the ligament to conform to an available space relieves pressure on an adjacent nerve.

Optionally, the method is applied to relieving symptoms of stenosis.

Optionally, the remodeling agent acts specifically on said ligament.

- 15 In an exemplary embodiment of the invention, there is provided a method of ligament remodeling, the method comprising:

- (a) applying energy to a ligament;
- (b) causing the ligament to conform to an available space.

Optionally, the method is applied to a spinal ligament in a spinal canal.

Optionally, the spinal ligament includes a Ligamentum Flavum (LF).

- 20 Optionally, the applying is directly to said ligament.

Optionally, the energy includes heat energy.

Optionally, the heat energy is applied by heating objects previously placed in said ligament.

Optionally, the energy includes ultrasonic energy.

- 25 Optionally, the energy includes radiofrequency energy.

Optionally, the radiofrequency energy is applied to objects previously placed in said ligament and causes said object to become heated.

BRIEF DESCRIPTION OF FIGURES

- 30 In the Figures, identical structures, elements or parts that appear in more than one Figure are generally labeled with the same numeral in all the Figures in which they appear. Dimensions of components and features shown in the Figures are chosen for convenience and clarity of presentation and are not necessarily shown to scale. The Figures are listed below.

Figs. 1 and 2 are diagrams of the spine illustrating anatomical features relevant to stenosis in general and ligament remodeling according to some embodiments of the invention in particular as well as potential placements for applicators of a remodeling agent according to various embodiments of the invention;

5 Fig. 3 is a flow diagram illustrating a sequence of events associated with performance of a method according some embodiments of the invention; and

Fig. 4 is a schematic representation of an energy delivery apparatus configured to deliver energy to a spinal ligament according to an exemplary embodiment of the invention .

10 DETAILED DESCRIPTION OF EMBODIMENTS

Remodeling methods

In an exemplary embodiment of the invention, a method of remodeling a ligament is provided. For purposes of illustration, remodeling of the Ligamentum Flavum (LF) according to methods of some embodiments of the invention will be
15 discussed in some detail with reference to relevant anatomical features of the spine.

Fig. 1 is a perspective view of a portion of a spine 100 illustrating the position of a spinal canal 120 relative to a pair of vertebrae 140 with an intervertebral disc 150, an LF 110 and a posterior longitudinal ligament 130. An anterior longitudinal ligament 135 is in the foreground in this view.

20 Fig. 2 is a top cross sectional view of spinal canal 120 showing in detail the relative positions of spinal cord 200, LF 110 and posterior longitudinal ligament 130. Anterior longitudinal ligament 135 is on top in this view. Spinal cord 200 contains both nerve fibers and spinal fluid and is fully surrounded by the Dura Mater (DM; 220). An epidural space 250 surrounds DM 220. In clinical cases of stenosis, LF 110
25 typically exerts pressure on spinal cord 200 through DM 220 and the spinal fluid. A small bone/ligament space 255 is believed to separate LF 110 from the vertebral bone surface.

A method 300 (Fig. 3) according to some exemplary embodiments of the invention typically begins with monitoring 310 of a clinical condition. If the clinical
30 analysis suggests that a ligament (e.g. LF 110) is exerting pressure on a nerve (e.g. spinal cord 200), the physician may consider ligament remodeling according to some embodiments of the invention. Optionally, imaging 320 of the affected area (e.g. spinal imaging) is conducted as an aid to clinical monitoring. Imaging may include,

for example X-ray, CT or MRI imaging. However, in many cases, significant clinical signs are present and their cause is not apparent in medical images. According to method 300, application 330 of a remodeling agent is performed, followed by additional monitoring 310 and/or imaging 320. Application 330 of the remodeling agent may be by various routes according to exemplary embodiments of the invention. In an exemplary embodiment of the invention, the ligament is caused to conform to an available space (e.g. in the spinal canal) after application of the remodeling agent. "Caused" as used herein includes, but is not limited to waiting and/or exercise and/or application of compresses (optionally hot and/or cold) and/or massage and/or physical therapy and/or chiropractic adjustment.

General application method

In an exemplary embodiment of the invention, application of the remodeling agent is via injection. Optionally, fluoroscopic guidance aids in inserting an injection needle to a desired location. Optionally, contrast dye may be injected to confirm location. In an exemplary embodiment of the invention, application 330 is conducted after contrast dye viewed in a fluoroscopic image indicates that the needle is in the correct position. The term application, as used herein, refers to application of a physical agent (e.g. a liquid) as well as to application of energy.

Exemplary administration routes:

A surgeon of ordinary skill will be able to apply the remodeling agent using, for example, one or more of the following administration routes. Consideration of the properties of the specific agent employed may influence the choice of administration route.

Application between ligament and bone

In an exemplary embodiment of the invention, application 330 is via injection between LF 110 and vertebra 140 into bone ligament space 255. Since bone and ligament are chemically very different, many remodeling agents which are selected because they are active against ligament will be characterized by negligible activity against bone. Optionally, the amount of remodeling agent applied is controlled, for example to prevent undesired contact of the remodeling agent with DM 220. Optionally, this embodiment provides greater dispersion of an injected remodeling agent with respect to the LF than injection into the same ligament as injected material

disperses through bone ligament space 255. Increased dispersion may cause remodeling to occur in a larger portion of the LF.

Intraligament application

5 In an exemplary embodiment of the invention, application 330 is via direct injection into LF 110. According to this embodiment of the invention, there is no strict requirement for tissue specificity in the selected remodeling agent so long as the application is carefully controlled to prevent contact of the remodeling agent with tissues other than the target ligament.

Epidural application

10 In an exemplary embodiment of the invention, application 330 is via injection into a lumen adjacent to a target ligament. In the context of spinal stenosis, application may be into epidural space 250 which surrounds DM 220. Because the applied remodeling agent is likely to contact tissues other than the target ligament, a tissue specific remodeling agent is optionally employed in this embodiment. In the
15 context of spinal stenosis, it is important to note that the LF and DM have significant chemical similarity. In an exemplary embodiment of the invention, a remodeling agent with significantly more activity on LF than DM is employed. Optionally, the agent acts primarily on a substrate which is specific to the LF.

Volume constraints

20 In exemplary embodiments of the invention which involve injection of a remodeling agent into or near a ligament, the remodeling agent is optionally supplied in a volume less than 1ml, optionally less than 500 μ l, optionally less than 250 μ l, optionally less than 100 μ l, optionally less than 50 μ l, optionally less than 25 μ l, optionally less than 10 μ l or intermediate volumes.

25 Alternatively or additionally, a controlled injection rate is employed, Suitable injection rates may be, for example, 500 μ l/min, 250 μ l/min, optionally less than 100 μ l/min, optionally less than 50 μ l/min or intermediate or greater values.

Optionally, injection of a protective material may be undertaken concurrently. For example, an epidural injection with a large volume of solution may be employed
30 to dilute and/or neutralize remodeling agents in order to protect, for example, the dura mater. Optionally, the solution may contain a buffer and/or an enzyme inhibitor (e.g. EDTA),

Clinical protocols

An important exemplary clinical context for method 300 is spinal stenosis. Typically stenosis patients exhibit debilitating clinical symptoms such as an inability to stand erect and/or ambulate. Because stenosis is often progressive, method 300
5 optionally includes repetition of clinical monitoring 310 and/or imaging 320 on a periodic basis after an initial application 330 of a remodeling agent.

Based upon the clinical condition of the patient and/or the imaging data, repetition of application 330 of the remodeling agent may be indicated. In an exemplary embodiment of the invention, reapplication 330 of a remodeling agent may
10 occur every 52 weeks, optionally every 32 weeks, optionally every 20 weeks, optionally every 12 weeks, optionally every 8 weeks or intermediate or greater intervals.

In an exemplary embodiment of the invention, each administration of a remodeling agent produces a similar effect per unit of remodeling agent as the
15 previous administration. This property will be referred to herein as “consistency”. Remodeling agents which work on a chemical or enzymatic basis are expected to perform consistently. For example, an enzyme employed as a remodeling agent will typically degrade its substrate in a predictable fashion which is determined primarily by the amount of enzyme; the amount of substrate and the buffering conditions.
20 Similarly, a particular physiologic substrate in a ligament is expected to undergo denaturation or dissolution under a known set of conditions. The physiologic substrate is not expected to alter its chemical properties to become “resistant” or immune” to these conditions. As a result, although it is difficult to predict if a treated ligament will continue to grow, it is expected that re-growth will include production of chemically
25 similar tissue which will be amenable to repeat treatment with the same remodeling agent. Lack of consistency is a problem with steroid hormones which were previously a main treatment alternative for stenosis.

In some cases, anti-inflammatory drugs (e.g. steroid hormones and/or NSAIDS) and/or pain relievers and/or anesthetics may be injected (or otherwise
30 administered) concurrently with a remodeling agent. This may, for example, prevent non-specific pain or inflammation associated with or caused by the injection procedure itself. Alternatively or additionally, the anti-inflammatory compounds

and/or pain relievers may act in combination and/or in synergy with the remodeling agent.

In an exemplary embodiment of the invention, method 300 is performed on an outpatient basis. Optionally no anesthesia is required. Optionally, only local
5 anesthesia is required. In an exemplary embodiment of the invention, patients are compliant with method 300. Optionally, patients are compliant because treatments are infrequent and/or there is no daily medication required between treatments. Optionally, patients are compliant because each treatment produces a clinical improvement which is perceived by the patient and/or caregivers. In an exemplary
10 embodiment of the invention, a patient and/or caregiver assumes at least partial responsibility for monitoring 310 and request an appointment for reapplication 330 of a remodeling agent when they perceive a change in the clinical situation. Monitoring 310 may be, for example, simple observation of an increased tendency to bend over and/or a decreased walking capacity and/or a perceived pain. The participation of
15 patients and/or caregivers in monitoring can be crucial to the success of method 300. This is especially true with regard to spinal stenosis where, in many cases, there is no apparent no difference in images of spine from an ambulatory patient and the same patient debilitated by stenosis a few weeks later. This lack of apparent difference in medical images indicates that only a small change on a target ligament by a
20 remodeling agent has the potential to produce a large clinical difference. In an exemplary embodiment of the invention, application 330 is performed before the overall clinical picture changes drastically.

For example, patients that walk erect and without pain after an initial application 330 of a remodeling agent are possibly best served if they monitor 310
25 their condition and return for re-application 330 of a remodeling agent when they perceive a slight discomfort when standing erect and/or notice a slight decrease in the distance they can walk without pain. At this stage, the affected ligament (i.e. LF 110) has only begun to cause pressure on the adjacent nerve (e.g. spinal cord 200). Optionally, intervention at this stage has a greater chance of success than a similar
30 intervention applied later when the clinical picture is more severe because the required degree of remodeling is less.

Remodeling agents

Remodeling agents may be generally divided into chemically based agents and energy. Examples of chemically based remodeling agents and energy based remodeling are presented here for illustration and do not limit the scope of the invention. Whether the remodeling employs a chemical agent or energy, it causes softening of the ligament and/or reduction in size and/or dissolution of a portion of the ligament. These changes may optionally alter ligament thickness and/or shape. The remodeling agents may be applied, for example, using one of the routes of administration described above. In an exemplary embodiment of the invention, the target area of the spinal ligament to which the agent is delivered is 0.5, optionally 1.0, optionally 2.0 optionally 3.0 square cm. in size or intermediate or lesser or greater areas.

Chemically based remodeling agents: pH based reagents

In an exemplary embodiment of the invention, a ligament is softened and/or shrunk and/or partially dissolved by application of an acid or a base. Alternatively or additionally, an acid or base may be applied to a ligament to denature one or more proteins in the ligament causing them to shrink. Examples of acids/bases suitable for use in this context include, but are not limited to, hydrochloric acid, acetic acid, phosphoric acid, sodium hydroxide and ammonia. The pH based reagents may be supplied, for example in a solution of water or normal saline. In an exemplary embodiment of the invention, a pH based reagent is supplied as a buffered solution so that it will maintain a defined pH after being applied to the target ligament and/or maintain a desired level of activity. A pH based remodeling agent may be supplied, for example, at a concentration of 5N or less, optionally 2.5N or less, optionally 1 N or less, optionally 0.5 N or less, optionally, 0.25 N or less optionally 0.1 N or less. Acid hydrolysis of relevant substrates may occur, for example, below pH 4.5, optionally below pH 3, optionally below pH 2 or intermediate or lesser pH values. Alkaline hydrolysis of relevant substrates may occur, for example, above pH 8.0, optionally above pH 9, optionally above pH 10 or intermediate or greater pH values.

In an exemplary embodiment of the invention, conditions are adjusted to produce a low molecular weight peptide which is optionally water soluble. Optionally, the molecular weight is less than 50,000, less than 25,000 or less than 10,000 Daltons.

In an exemplary embodiment of the invention, these small molecular weight peptides are subject to diffusion within the body.

According to various exemplary embodiments of the invention, hydrolysis may be induced locally in a pattern of spots or stripes so that the overall strength of the ligament is not compromised. Alternatively or additionally, a target zone of the ligament is selectively weakened and repeat treatments, if performed, are to this same target zone.

Exemplary chemically based remodeling agents: Malondialdehyde

Collagen has enzyme-catalyzed cross-links formed between its individual molecules that are essential for maintaining the structure and flexibility of the collagen fiber. The cross-link dehydro-hydroxylysino-norleucine reacts irreversibly with 10 mM malondialdehyde at least 3 orders of magnitude faster than glucose reactions with lysine or arginine, such that there is little cross-link left after 1 h at 37 degrees C. Other cross-links and glycated elements of collagen are also vulnerable to this reaction. (Slatter et al. (1999) J Biol Chem, Vol. 274, Issue 28, 19661-19669; fully incorporated herein by reference). Although it has not been specifically investigated with regard to the LF, Malondialdehyde seems capable of altering LF physical properties by altering properties of an LF collagen component in a way that would facilitate remodelling.

Malondialdehyde is only one exemplary remodeling agent of this class. It is expected that as the chemical composition of the LF in general, and the stenotic LF in particular, is more thoroughly characterized, additional remodelling agents which affect specific crosslink types will be characterized.

Chemically based remodeling agents: Enzyme based reagents

In an exemplary embodiment of the invention, an enzyme with specificity for a substrate found in the target ligament is employed as a remodeling agent. Optionally, action of the enzyme on its substrate causes softening or partial dissolution or shrinking of at least a portion of the target ligament. According to various exemplary embodiments of the invention, collagen type II and/or collagen type X and/or S100 protein and/or Pentosidine and/or chondroitin-6-sulfate and/or other high molecular weight proteoglycans are suitable enzyme substrates. These compounds are suitable enzyme substrates because their levels increase in the LF during the clinical progression of stenosis. In an exemplary embodiment of the

invention, a remodeling agent includes an enzyme with specificity for a substrate found in the LF and found to a lesser degree, or only in negligible quantities, in the DM.

5 A procedure for enzymatic digestion of intervertebral discs called chemonucleolysis is well known in the art. M. D. Brown reviewed the status of chemonucleolysis (1996; Spine 21[24 Suppl]: 62S-68S) and concluded that the use of chymopapain is a safe and effective alternative to surgical disc excision. Brown reported that efficacy of chymopapain has been shown controlled trials with a minimum 10-year follow-up period. Brown also reported that clinical studies with
10 collagenase and laboratory studies with chondroitinase ABC have shown that chemonucleolysis can be performed with enzymes other than chymopapain. Takegami et al. (Spine J. (2005) 5(3):231-8) later confirmed the efficacy of chondroitinase ABC in chemonucleolysis. The Brown and Takegami references are fully incorporated herein by reference.

15 In an exemplary embodiment of the invention, enzymes suitable for use as remodeling agents may be obtained in purified form from chemical suppliers. An example of such a commercially available enzyme is Collagenase type I (C6885; Sigma-Aldrich; St Louis MO; USA). Collagen type I in the LF is well correlated with the clinical progression of stenosis.

20 Enzymes applied to a target ligament are capable of diffusion, especially if they are applied adjacent to the ligament, as opposed to injected directly into the ligament. The probability of diffusion increases with time. Alternatively or additionally, enzymes may exhibit increased nonspecific activity in the absence of sufficient quantities of their nominal substrate. Alternatively or additionally, method
25 300 may have as its objective modification of only a fraction of the molecules of a specific chemical species in a target ligament. In an exemplary embodiment of the invention, an enzyme with autocatalytic activity is employed as a remodeling agent. Optionally, an autocatalytic enzyme digests itself before it can diffuse to a significant degree and/or digests itself in the absence of sufficient quantities of its nominal
30 substrate and/or digests itself in the presence of its nominal substrate so that only a portion of the nominal substrate is digested. In an exemplary embodiment of the invention, 50%, optionally 25%, optionally 10% optionally 5%, optionally 1% or greater or lesser or intermediate percentages of the nominal enzyme substrate are

digested before an applied enzymatic agent loses its activity because of dilution and/or diffusion and/or autocatalysis.

Optionally, enzyme based remodeling agents are supplied in a formulation which insures pH and/or ionic conditions that produce a desired level of activity. For example, enzymes may be supplied in a buffered solution with a defined pH. Optionally, this defined pH may be selected to insure maximum enzymatic activity or sub-maximal enzymatic activity. Alternatively or additionally, the buffer may include ions and/or chelating agents. In an exemplary embodiment of the invention, a collagenase is supplied in a buffer including 5, optionally 10, optionally 25 millimolar or lesser or greater or intermediate concentrations of Calcium to insure collagenase activity. The Calcium may be supplied, for example as a chloride, phosphate or bicarbonate salt.

In an exemplary embodiment of the invention, an applied remodeling agent has an activity which is partly due an enzymatic activity and partly due to a pH of the applied material.

Energy based remodeling agents: light

In an exemplary embodiment of the invention, a beam of light energy, optionally laser light energy, is applied to a selected portion of a target ligament to cause remodeling. Optionally, the applied light energy causes softening or partial dissolution or shrinking of at least a portion of the target ligament. Light may be conducted to the target ligament, for example, by use of a fiber optic device.

Treatments of this type have been employed in cosmetic surgery of the skin, http://www.skinpilot.de/1024/Willkommen_engl/Uebersicht_engl/Altern_engl/Mechanische_Schaelbehandlung_e/body_mechanische_schaelbehandlung_e.html where a high-energy concentrated beam of light is aimed at the skin tissue. As the energy is released in the form of ultra-short pulses (e.g. ultra-pulsed CO₂ or erbium YAG laser) and the movement is controlled by computer, the laser energy and therefore also the depth of treatment can be very well controlled. The treatment causes collagen fibers to contract and/or shrink. A CO₂ laser produces heating to a greater depth and produces a more marked collagen shrinking. Depending upon the type of laser employed, an optional waveguide may be employed to focus the applied energy on a desired target.

Energy based remodeling agents: heat

In an exemplary embodiment of the invention, heat energy is applied to a selected portion of a target ligament to cause remodeling. Optionally, the applied heat energy causes softening or partial dissolution or shrinking (e.g. by burning or
5 denaturing) of at least a portion of the target ligament. Heat may be delivered, for example, by application of an electric current through a wire held in proximity to the target ligament. The exact degree of heat required may vary with the target ligament and/or the specific type of remodeling desired. For example, a portion of a target ligament may be heated to the denaturation point of a specific protein known to be
10 causative of a particular clinical symptom (e.g. type X collagen in the case of stenosis). This will also cause denaturation of proteins which are denatured below the denaturation point of the specific protein selected.

In the shoulder, electrothermal arthroscopic capsulorrhaphy (ETAC) causes thermal shrinkage of redundant capsular tissue to tighten the joint and may be
15 employed in lieu of surgery (Mohtadi et al. Trials 2006, 7:4 doi:10.1186/1745-6215-7-4 <<http://www.trialsjournal.com/content/7/1/4>>; the disclosure of which is fully incorporated herein by reference) The technique is performed with commercially available equipment such as ETAC probes (Oratec Vulcan Generator electro-thermal system; Oratec Interventions Inc., Menlo Park, CA, USA).

20 An alternate device for localized heat delivery is the "Tissue LinkEndoFB3.0 (tissue Link Europe s.r.l.; San Damiano d'Asti; Italy; described in Min Invas Ther & allied Technol (2002) 11(5/6):265-27; the disclosure of which is fully incorporated herein by reference) which employs an electric current delivered through a continuous flow of saline applied at a low flow rate. The saline serves to both localize the applied
25 electrical current and assure that it penetrates the target tissue. Devices of this type may be useful, for example, in bone ligament space 255. Heating of type I collagen to 60-100 degrees C can shrink the collagen to roughly half of its original size. Similar devices may also be used to deliver RF energy to heat deep tissue.

US 6,976,492 to Ingle et al. discloses devices, methods, and systems for
30 shrinking of collagenated tissues. This patent is fully incorporated herein by reference. Ingle teaches tissue contraction resulting from controlled heating of the tissue by affecting the collagen molecules of the tissue. Contraction occurs as a result of heat-induced uncoiling and repositioning of the collagen λ -pleated structure. Ingles teaches

protocols which produce significant tissue contraction without substantial collateral tissue damage. Specifically, Ingles discloses heating the target tissue to a value in the range from about 60° C. to 110° C., optionally in the range from about 60° C. to 80° C. This can produce shrinkage of the target tissue in at least one dimension of
5 between about 20 and 50 percent. Optionally, heating energy is applied for a period of from 30 seconds to 5 minutes. Heating times may vary with electrode configuration. In an exemplary embodiment of the invention, a heat time of about 5 minutes is appropriate for an electrode separation of about 4 cm. Shorter heat times may be used with smaller electrode separation distances. Ingles discloses that the temperature of
10 adjacent (non target) tissue is maintained at about 45° C or less. For treatment of the LF, smaller electrode separation distances (e.g. 5 to 10 mm) and shorter times (e.g. 1 minute or less) are envisioned. Reducing electrode separation distance and or time can serve to reduce collateral tissue damage to a level which is acceptable even in a delicate spinal procedure.

15 It may be desirable to repeat the remodeling process at intervals if clinical signs recur after treatment. In an exemplary embodiment of the invention, repeat remodeling using heat energy may be facilitated by implanting metal seeds in a target ligament. These seeds may serve to focus heat resulting from applied radiofrequency (RF) energy to a desired location. For example, using a 1MHz RF signal, a 1 mm
20 diameter sphere of a suitable metal (e.g. titanium or stainless steel) could serve to accumulate energy and cause localized heating relative to surrounding tissue. The degree of heating achieved would vary with the duration of the applied RF signal. Optionally, use of seeds permits RF energy to be applied from an external source, as opposed to an internal probe. An additional advantage of seeds is that they are visible
25 in X-ray and/or ultrasound images. This property permits implantation of a seed in a desired target location followed by specific heating of the seed from an extracorporeal energy source.

Energy based remodeling agents: ultrasound (US)

30 In an exemplary embodiment of the invention, ultrasound energy is applied to a selected portion of a target ligament to cause remodeling. Optionally, the applied US energy causes softening or partial dissolution or shrinking (e.g. by burning or denaturing) of at least a portion of the target ligament. US energy may be delivered, for example, by insertion of a US probe in proximity to, or into, the target ligament.

The applied US energy may remodel the ligament by breaking chemical bonds directly (e.g. shortening polymer length and/or reducing a degree of cross-linking) and/or by causing heating of the target ligament. The exact degree of US energy required may vary with the target ligament and/or the specific type of remodeling
5 desired. For example, a portion of a target ligament may be subject to a US regimen designed to break off certain types of side chains. For example, in the case of spinal stenosis, a US protocol which reduces the amount of Pentosidine by de-glycating Pentosidine molecules might be employed to the LF.

Energy delivery apparatus

10 Fig. 4 is a schematic representation of an exemplary energy delivery apparatus 400 configured to deliver energy to a spinal ligament. The pictured apparatus 400 delivers energy to a spinal ligament through one or more energy outlets 435 mounted on a working head 430. Although ten energy outlets 435 are pictured as an example, the exact number is not critical to the operation of device 400 so long as outlets 400
15 are capable of delivering sufficient energy to a desired area of the target ligament. As few as one outlet 435 or as many as hundreds, or thousands, of outlets 435 may be employed in various embodiments of the invention. In an exemplary embodiment of the invention, the target area of the spinal ligament to which energy is delivered is 0.5, optionally 1.0, optionally 2.0 optionally 3.0 square cm. in size or intermediate or
20 lesser or greater areas.

According to various embodiments of the invention, the energy to be delivered may be light, ultrasonic waves, RF energy or microwaves.

In an exemplary embodiment of the invention, working head 430 is inserted to a target zone (e.g. bone ligament space 255 or epidural space 250; see Fig. 3) in an
25 arthroscopic procedure. Such an arthroscopic procedure may be facilitated by use of a spinal cannula 420 with an inner lumen. In an exemplary embodiment of the invention, working head 430 is collapsed and stored in a distal portion 425 of cannula 420 during arthroscopic insertion. Optionally, the arthroscopic insertion is monitored, for example by fluoroscopy or ultrasonic imaging, and working head 430 is ejected
30 and/or expanded after distal portion 425 of cannula 420 is in a desired location. In order to facilitate storage in a lumen of cannula 420, working head 430 may be constructed of an elastic or plastically deformable material. For example, an elastic

working head 430 may be stored in the lumen and ejected by pushing with a tamping rod inserted through the lumen.

Once working head 430 is deployed, controller 410 delivers an operational signal to energy outlet(s) 435 so that they deliver energy to the target ligament. The energy may be delivered, for example, via a conductive wire or fiberoptic strand passed through cannula 420 to working head 430 and connected to energy outlets 435. According to various embodiments of the invention, outlets 435 may be energized synchronously or sequentially. According to various embodiments of the invention, outlets 435 may be energized with a uniform degree of energy or with varying degrees of energy. Alternatively or additionally, energy may be delivered continuously or in pulses separated by intervals. In an exemplary embodiment of the invention, the rate of energy delivery may be controlled by varying pulse amplitude and/or interval duration.

In an exemplary embodiment of the invention, controller 410 contains a user input device (e.g. keypad or operational knob with a scale) or is connectable to a device equipped with such an input (e.g. computer, PDA or cellular telephone). Optionally, two or more parameters selected from among energy amplitude, energy frequency, duration of energy pulse, firing pattern for energy outlets 435 and duration of pause between energy pulses are independently adjustable.

In an exemplary embodiment of the invention, one or more sensors 437 are provided (one is pictured). Sensor 437 serves to measure the amount of energy delivered and/or the effect of that energy on the target tissue and/or the amount of energy delivered to adjacent non-target tissue. Optionally, sensor 437 is a thermometer which measures a temperature of a target ligament. In an exemplary embodiment of the invention, sensor 437 serves to close a feedback loop with controller 410 and energy outlets 435. For example, if the objective of the treatment is to denature a ligament component by heating it to 63 degrees centigrade, controller 410 could be programmed to step down energy delivery when sensor 437 indicates a local temperature of 61.5 degrees and cease energy delivery after the target temperature of 63 degrees is reached. Optionally, measurements conducted by sensor(s) 437 in a non-target tissue may be used in implementation of a negative feedback loop as a safety pre-caution.

General

In an exemplary embodiment of the invention, a remodeling agent according to the invention is supplied as a pharmaceutical composition formulated as a pharmaceutical composition for use in/on the LF. The pharmaceutical composition includes a physiologically effective amount of at least one remodeling agent (e.g. chemical and/or enzymatic) together with carriers and/or buffers and/or excipients. Optionally, the pharmaceutical composition is supplied as a sterile injectable preparation and/or a sterile crystalline preparation ready for dilution with a sterile diluent.

10 In an exemplary embodiment of the invention, the pharmaceutical composition is provided as an article of manufacture comprising packaging material and instructions for use in the treatment of stenosis. The instructions may include, for example, dosage recommendations and/or suggested routes of administration.

15 In an exemplary embodiment of the invention, the article of manufacture includes one or more unit dosage forms, optionally loaded and ready for use.

In an exemplary embodiment of the invention, an energy delivery apparatus according to an exemplary embodiment of the invention is provided as an article of manufacture comprising packaging material and instructions for use in the treatment of stenosis. The instructions may include, for example, suggested treatment protocols and/or suggested routes of administration. The treatment protocols may be expressed, for example, in terms of time and temperature.

20 In an exemplary embodiment of the invention, a remodeling agent according to an exemplary embodiment of the invention is used in conjunction with an indirect decompression treatment for scoliosis. Exemplary indirect decompression treatments include, but are not limited to Dynesis and the X stop which attempt to indirectly decompress the stenosis without doing a laminectomy.

30 In the description and claims of the present application, each of the verbs “comprise”, “include” and “have” as well as any conjugates thereof, are used to indicate that the object or objects of the verb are not necessarily a complete listing of members, components, elements or parts of the subject or subjects of the verb.

The invention has been described using detailed descriptions of embodiments thereof that are provided by way of example and are not intended to necessarily limit the scope of the invention. In particular, numerical values may be higher or lower than

ranges of numbers set forth above and still be within the scope of the invention. The described embodiments comprise different features, not all of which are required in all embodiments of the invention. Some embodiments of the invention utilize only some of the features or possible combinations of the features. Variations of embodiments of the invention that are described and embodiments of the invention comprising different combinations of features noted in the described embodiments can be combined in all possible combinations including, but not limited to use of features described in the context of one embodiment in the context of any other embodiment. The scope of the invention is limited only by the following claims.

10 All publications and/or patents and/or product descriptions cited in this document are fully incorporated herein by reference to the same extent as if each had been individually incorporated herein by reference.

CLAIMS

1. A pharmaceutical composition, the pharmaceutical composition comprising:
 - (a) an active ingredient including a physiologically effective amount of a remodeling agent capable of altering properties of a Ligamentum Flavum (LF) so that the LF conforms to an available dimension of a spinal canal; and
 - (b) a pharmaceutically acceptable carrier, diluents and excipients.
2. A pharmaceutical composition according to claim 1, supplied as an article of manufacture additionally comprising:
 - (c) packaging material and
 - (d) instructions for use in remodeling of the LF.
3. An article of manufacture according to claim 2, supplied as a unit dosage form.
4. A unit dosage form according to claim 1 or 2, additionally comprising at least a portion of a tool for locally applying said remodeling agent to said LF.
5. A pharmaceutical composition according to any of the preceding claims, wherein said remodeling agent includes at least one chemical capable of locally adjusting a pH of at least a portion of the LF.
6. A pharmaceutical composition according to any of the preceding claims, wherein said remodeling agent includes an enzyme.
7. A pharmaceutical composition according to claim 6, wherein said enzyme digests a substrate in the LF.
8. A pharmaceutical composition according to claim 6, wherein said enzyme has negligible effect on substrates found in a dura mater in proximity to the LF.

9. A pharmaceutical composition according to any of the preceding claims, wherein said alteration of properties refers to softening.
10. A pharmaceutical composition according to any of the preceding claims, wherein said alteration of properties refers to partial dissolution.
11. A method of spinal ligament remodeling, the method comprising:
 - (a) applying a ligament remodeling agent to a spinal ligament;
 - (b) causing the spinal ligament to conform to an available space.
12. A method according to claim 11, applied to a spinal ligament in a spinal canal.
13. A method according to claim 11 or 12, wherein said spinal ligament includes a Ligamentum Flavum (LF).
14. A method according to any of claims 11-13, wherein said applying is directly to said ligament.
15. A method according to any of claims 11-14, wherein said applying is by injection into said ligament.
16. A method according to any of claims 11-15, wherein said causing the ligament to conform to an available space relieves pressure on an adjacent nerve.
17. A method according to any of claims 11-16, applied to relieving symptoms of stenosis.
18. A method according to any of claims 11-17, wherein said remodeling agent acts specifically on said ligament.
19. A method of spinal ligament remodeling, the method comprising:
 - (a) applying energy to a spinal ligament;
 - (b) causing the ligament to conform to an available space.

20. A method according to claim 19, applied to a spinal ligament in a spinal canal.
21. A method according to claim 20, wherein said spinal ligament includes a Ligamentum Flavum (LF).
22. A method according to any of claims 19-21, wherein said applying is directly to said ligament.
23. A method according to any of claims 19-22, wherein said energy includes heat energy.
24. A method according to any of claims 19-23, wherein said heat energy is applied by heating objects previously placed in said ligament.
25. A method according to any of claims 19-24, wherein said energy includes ultrasonic energy.
26. A method according to any of claims 19-25, wherein said energy includes radiofrequency energy.
27. A method according to any of claims 19-26, wherein said radiofrequency energy is applied to objects previously placed in said ligament and causes said object to become heated.

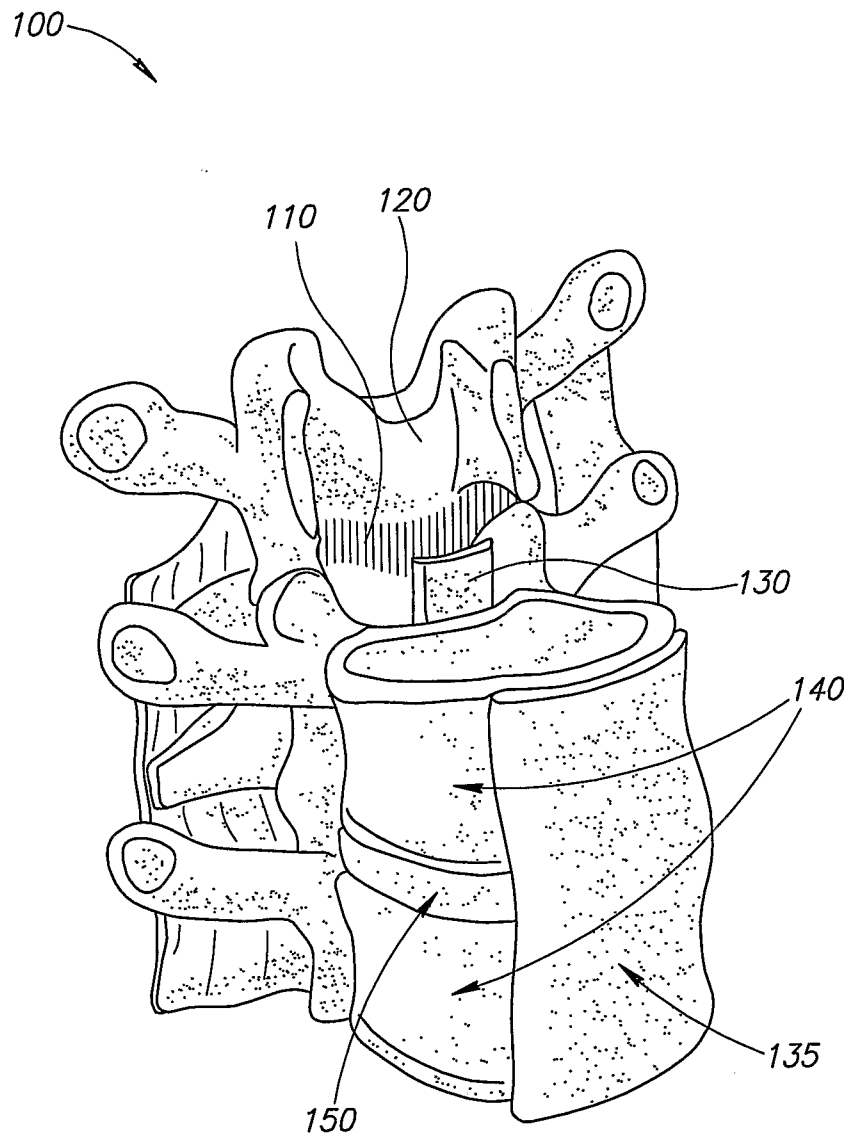


FIG.1

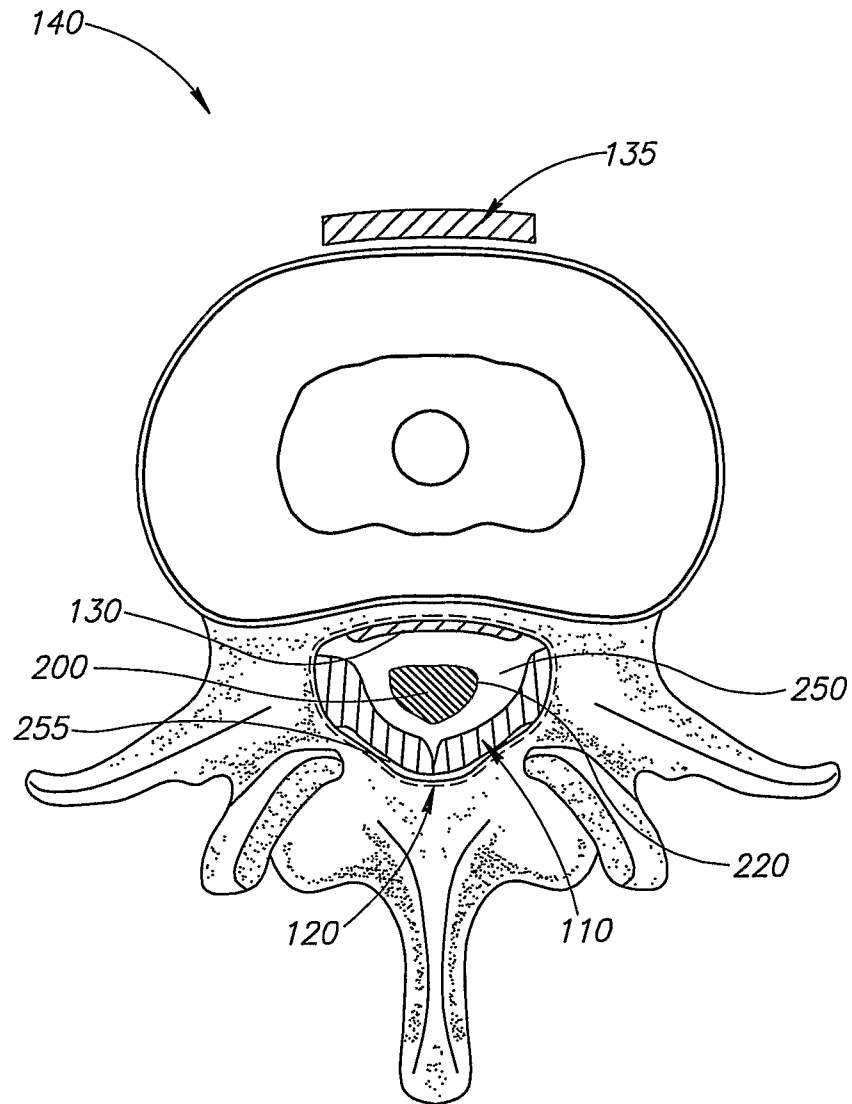


FIG. 2

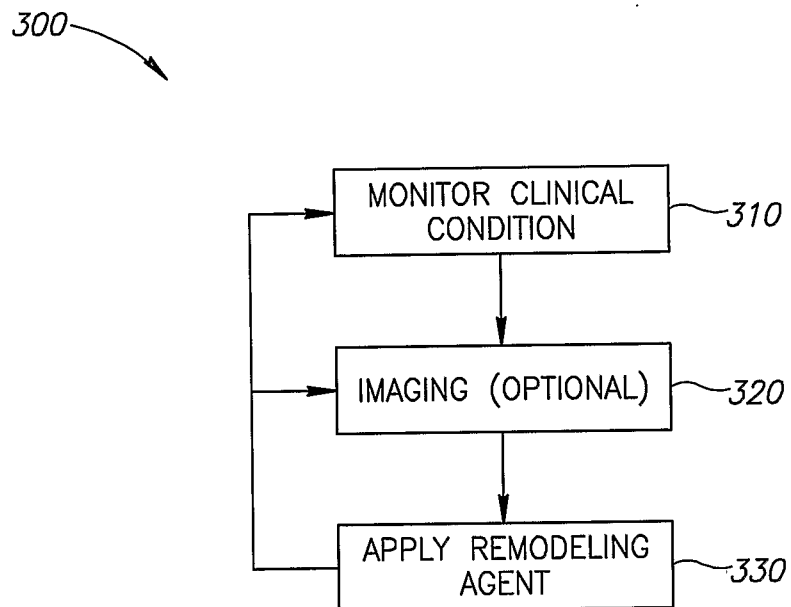


FIG.3

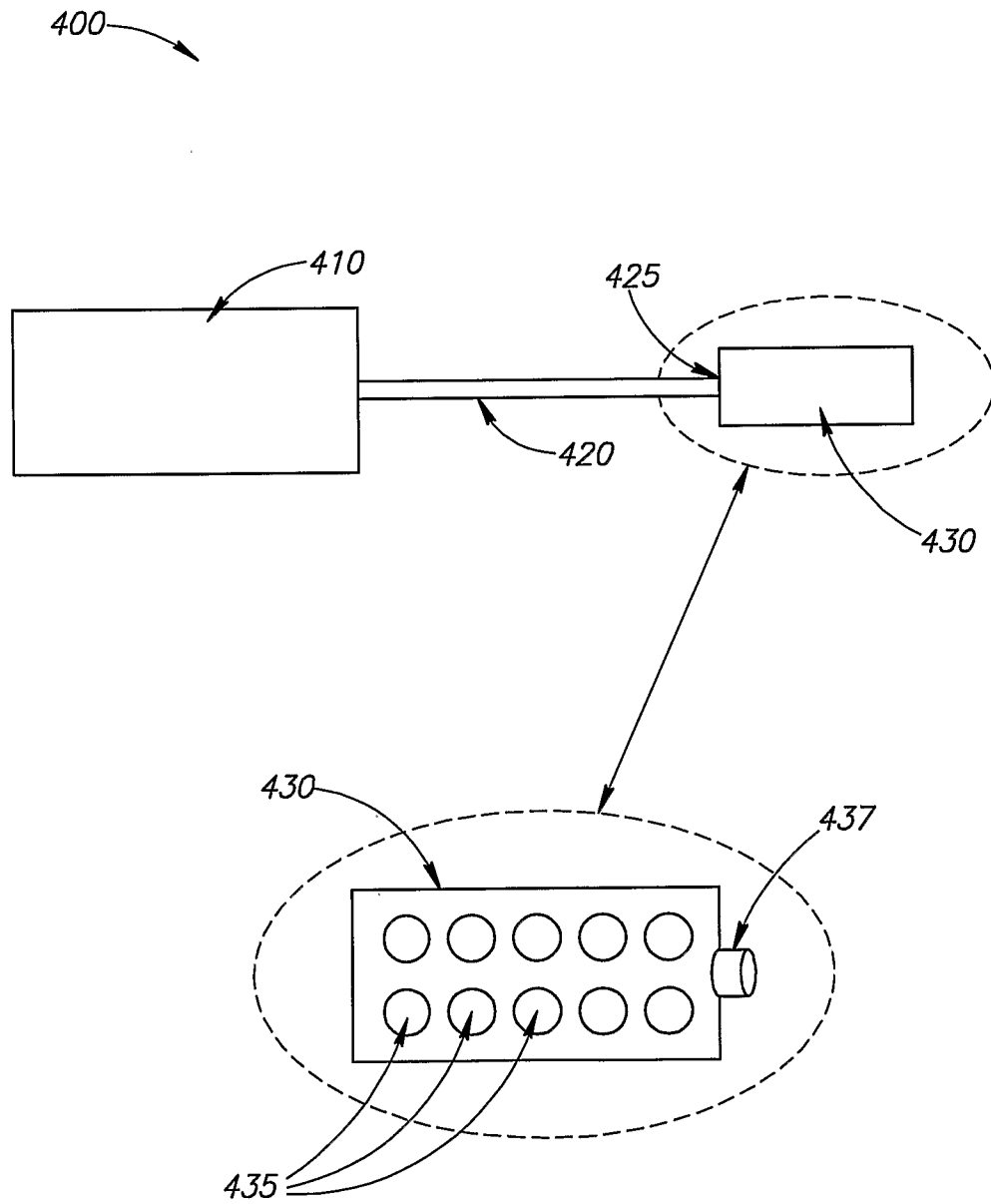


FIG. 4