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(54) Title: MEDICAL DEVICE FOR DELIVERY AND/OR EXTRACTION OF MATERIAL

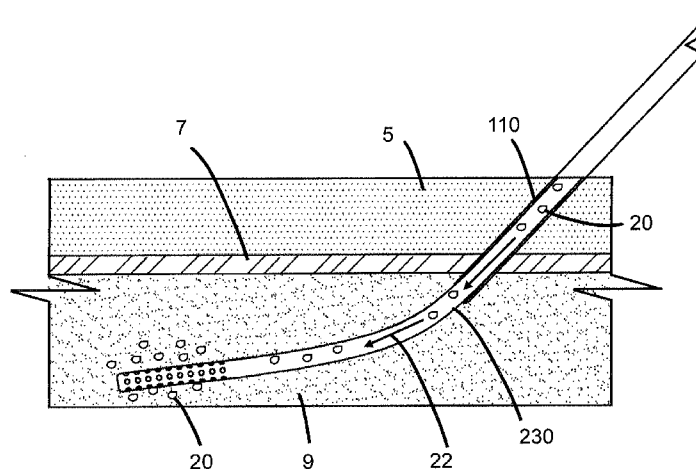


Fig. 8

(57) Abstract: Systems and methods for delivery and collection of materials to and from a target site within bone, preferably an intrasosseous space. A penetrating member includes a sharp tip for piercing tissue, and is interconnected to a driving actuator and is axially oscillated for insertion and/or removal from the bone. A transfer member having a transfer member lumen is positionable through the penetrating member and includes a plurality of apertures through which materials may be delivered to or collected from the target site. A reinforcing member may be removably positioned within a penetrating member lumen for mechanical rigidity and heat exchange, and a guide member may be disposed within a transfer member lumen for additional support during insertion and removal. Materials such as stem cells, HSCs, bone marrow, lentiviral vectors, gene therapies, and other materials can be delivered and/or collected from the target site.



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Medical Device for Delivery and/or Extraction of Material

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application claims the benefit of co-pending United States Provisional
5 Application Serial No. 62/356,915, filed on June 30, 2016, and United States Provisional
Application Serial No. 62/360,635, filed July 11, 2016, the contents of which are incorporated
herein by reference in their entireties.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

10 This invention was made with government support under CA139774 awarded by the
National Institutes of Health. The government has certain rights in the invention.

FIELD OF THE INVENTION

The present invention generally pertains to intraosseous bone access and delivery of
materials such as stem cells and gene therapies directly to the bone marrow or extraction or
15 collection of materials therefrom. Specifically, the invention relates to systems and methods
including handheld medical devices having penetrating members driven by axial oscillating
vibration and/or rotation to reduce the penetration forces needed to pierce bone, and delivery or
collection of material to or from the intraosseous space or other tissue beyond the bone for
beneficial and/or therapeutic use.

20 BACKGROUND

Many medical procedures require the delivery or collection of material from a patient.
However, access to locations deep within the body, such as intraosseous access to the bone, is
often very difficult for the healthcare practitioner and painful for the patient. It may be
necessary to access the inside of cortical bone or bone marrow, such as to provide life-saving
25 fluids when IV use is not an option. Direct introduction of other materials, such as therapeutic
compounds or drugs directly to a particular target site would be beneficial, but accessing tissues
deep within the body remains difficult and painful.

Examples of intraosseous access procedures include but are not limited to biopsy, bone
marrow transplant, emergency fluid infusion, stem cell delivery, and DNA modifying vector

techniques. A major disadvantage for intraosseous procedures is the force required to penetrate the bone tissue. For example, typical biopsy tools include a handle and hollow cannula into which a solid stylet is inserted that attaches to the handle. To penetrate through cortical bone, a healthcare practitioner grasps the handle and twists the cannula and stylet through the bone to the marrow. The distal tip of the inner stylet or trocar is often sharpened and has an angled chisel-like face which reduces the surface area to reduce the exertion force. Despite this design, taking bone biopsies still requires a great deal of force to penetrate the bone tissue. Pain is minimized with proper local anesthesia, though the patient can still experience discomfort due to a pressure sensation during insertion and retraction. Possible complications include bleeding, pain, and infection. The penetration force can also be tiring for clinicians and lead to multiple sampling attempts, thereby increasing the risk of complications. Another problem is crushing the sample or being unable to retrieve part or all of it, limiting the ability to diagnose.

In addition to the high force necessary to penetrate bone, healthcare practitioners are also limited by the angle of insertion. When the needle forms a right angle with respect to the surface of the bone, the needle tip can easily be anchored within bone. As the angle between the needle and the surface of the bone moves from 90 to 0 degrees, the risk of slipping off the bone and damaging nearby tissues increases. For bone marrow or bone lesion sampling in anatomical sites such as the rib or arm, being able to sample at oblique angles would allow for longer samples to be obtained with fewer insertion sites.

Another challenge with intraosseous access is directing therapeutic materials to specific anatomical target sites. For example, in bone marrow (BM) transplantation, hematopoietic stem cells (HSCs) are typically harvested from either a patient's or donor's BM or peripheral blood, processed ex vivo, and delivered back to the patient (recipient) via intravenous (IV) infusion. Infusion of autologous (patient cells) or allogeneic stem cells (donor cells) is used to re-establish hematopoietic function in patients whose bone marrow or immune system is damaged or defective. Transplanted hematopoietic stem cell (HSC) require a specialized environment to survive and proliferate (e.g., HSC niche). Presently, HSCs are transplanted by and infusion of HSCs by IV infusion following myeloablation, upon which the HSCs travel through the blood and settle within the BM where they can engraft and proliferate, a process known as homing. Unfortunately, this approach is associated with loss of the majority of the

HSC as many of them do not reach the niche in the bone marrow and die in other organs such as lung and liver, where they cannot survive and proliferate. Additionally, IV infusion of stem cells is correlated with graft-versus-host disease (GvHD), a condition where immune cells from the delivered stem cells attack the recipient's cells.

5 Myeloablation (e.g., conditioning of the patient) is typically required to eliminate the endogenous HSC which are defective or tumoral. In the case of gene therapy, for some disorders it could be sufficient to perform reduced myeloablation and achieve partial chimerism. In other words, not all the endogenous defective HSC need to be removed, as only a portion of modified HSC may be sufficient to correct the phenotype of the patient. This is
10 defined as partial chimerism (when donor cells and host cells are present at the same time after HSCT) or partial transgenic chimerism (when genetically modified and defective HSCs are present at the same time after HSCT).

 Presently, gene therapy clinical trials require ex-vivo modification of the HSC, before they can be infused into the patients. Gene transfer is normally required only for HSC, as the
15 other hematopoietic cells are short lived and do not contribute to the long-term correction of the patient. Correction of the HSC requires harvesting the HSCs from the patient and treating them with the gene therapy vector (transduction). Before these corrected HSCs are reinfused, myeloablation of the patient is required. This is followed by hospitalization of the patient, as he or she needs to recover from myeloablation. Often patients require blood or platelet
20 transfusions following myeloablation, as some of the consequences of the conditioning are anemia and bleeding. Additional issues include, for example, infection and sterility.

 Currently, an excess of processed HSCs and preconditioning regimens are needed to accommodate inefficient IV HSC delivery. Preconditioning is the process of delivering myelosuppressive chemotherapy such as busulfan and cyclophosphamide to inhibit the
25 recipient's native bone marrow and promote the BM microenvironment for engraftment of the delivered HSCs. However, preconditioning increases the risk of serious complications such as infection and death. Delivering a larger volume of processed HSCs and/or preconditioning is not tolerable or feasible for many potential therapy candidates. The required dosage of HSCs and preconditioning regimen depends upon the patient's physical characteristics, diagnosis,
30 and reaction to the therapy. Direct intraosseous (IO) injection of therapies to the BM has been explored as a way to improve homing to BM and reduce GvHD, however, current IO delivery

has not shown consistent improvement in hematopoietic recovery. One possible theory for the limited benefit from the current IO approach is that existing BM aspirate needles deliver therapies to a concentrated area at the BM aspirate cannula tip, resulting in high flow rates and pressures during injection. These pressures exceeding diastolic pressure then result in the immediate escape of delivered HSCs into the vascular system, resulting in less targeted delivery to the desired BM microenvironment.

A need therefore exists to be able to use less force to penetrate hard tissue such as the cortical bone at low inclination angles. This would reduce clinician fatigue, patient discomfort, and tissue damage while improving the sampling success rate and quality. Additionally, a device is needed that can directly deliver materials such as therapies to specific sites within bone which would improve engraftment.

SUMMARY

The present invention is directed to a system and method for intraosseous access and delivery and collection of materials to a target area within biological tissue, preferably osseous tissue. The system includes a penetrating member such as a rigid cannula, a driving actuator that provides oscillating motion such as axial and/or rotational vibrations to the penetrating member, and a transfer member that is flexible and has a plurality of apertures at a distal end through which materials such as stem cells, HSCs, gene therapies, bone marrow and blood may flow for delivery and/or extraction. The present invention also provides a reduction in heat at the penetrating member and/or target site to avoid deleterious effect to the target site tissue and/or material being delivered, so the cells or other material may remain viable once intraosseous access is gained, both for delivery and/or extraction of materials.

The penetrating member is preferably rigid, and may be a needle or cannula with a lumen running through the full length of the member. A reinforcing member may be included, and may be a solid needle with a sharp tip at the distal end. The reinforcing member fits coaxially within the lumen of the penetrating member, and together they are inserted through bone, and may in some instances be inserted first through the outer layer of bone, such as cortical bone, to access the target site, which may be inner tissues such as bone marrow. Once the target site reached, the reinforcing member is removed, leaving the penetrating member as

a channel to the tissue access site. In some embodiments, only a penetrating member is used for insertion, and no reinforcing member is needed.

5 A driving actuator is preferably located in a handpiece and is coupled to the penetrating member and/or reinforcing member. The driving actuator provides axially oscillating vibrations to the penetrating member and/or reinforcing member. The driving actuator, which may be a piezoelectric motor, electromagnetic motor, Langevin or flextensional transducer, operates in the range of 1 Hz – 80 kHz and generates axial displacement of the penetrating member in the range of 0.1 – 100 μ m. This vibration disrupts the tissues and reduces the force needed to penetrate the tissues, such as bone, as a result of this oscillatory vibration. The
10 handpiece containing the driving actuator can be used for guiding the penetrating member, reinforcing member and/or guide member discussed below into and out of the tissue, such as bone.

Once the penetrating member has pierced the bone, a transfer member such as a catheter is fed through the lumen of the penetrating member. The transfer member has a plurality of
15 apertures extending through the wall of the member at the distal end. In one embodiment, at least a portion of the transfer member is made of a flexible material so it is deflectable within the target site and/or the penetrating member. Preferably, at least the distal tip of the transfer member is flexible, but the entire length of the transfer member may be flexible.

The transfer member is fed through the lumen of the penetrating member until the tip
20 of the catheter is exposed in the tissue site. Material such as stem cells, HSCs, lentiviral vectors, drugs, fluids, and therapeutic agents may be delivered through the transfer member through the apertures into the surrounding target site. Delivery material may occur by any method of fluid dynamics, including diffusion or pressure differential such as created by depressing the plunger of a syringe at the proximal end of the transfer member. Collection of
25 material may occur through aspiration through the transfer member. The transfer member can slide freely within the penetrating member. Because of this, the healthcare practitioner can easily adjust the length of the transfer member protruding from the penetrating member to ensure the fluid is delivered or collected at a specific site. As the length of the transfer member beyond the tip of the penetrating member is increased, the amount of cells that are able to be
30 accessed are increased in tandem. In the cases where the transfer member is curved or flexible, the tip may be inserted into the target site and then rotated to increase the target area radially.

In some embodiments, a guide member may be employed within the transfer member to provide rigidity, such as to penetrate tough tissue such as the spongy bone where marrow resides. The guide member is solid, lacking an internal lumen, and may be straight or at least partially curved. The guide member may be manually inserted into the transfer member either before or during insertion into the penetrating member and/or target site, and in some embodiments may be attached to the handpiece to receive oscillating vibrations to assist in accessing the target site. Once the transfer member is in place, the guide member may be removed to allow materials to be delivered or collected through the transfer member.

The system described herein can be used to penetrate hard tissue such as cortical bone at oblique angles by employing the handpiece to vibrate the penetrating member and reinforcing member during insertion. As the penetrating and reinforcing members vibrate against bone, tissue bonds are broken. The resulting fragments of bone are cleared as the healthcare practitioner twists the handpiece back and forth. The removal of tissue in front of the penetrating member path allows the distal tip to be advanced through the outer layer of bone with reduced force. Reduced insertion force also allows healthcare practitioners to enter bone at oblique angles since the high forces that usually cause the penetrating member to slip off the bone are no longer necessary. Instead, the penetrating member can be directed at the desired angle as the handpiece does the work of vibrating the penetrating member into the bone.

In addition, the invention includes methods of delivery of material such as therapies to specific sites within bone. Materials are currently delivered through cannulas, but adjusting the cannula position to target a specific site often requires altering the position of the cannula lodged within bone or reinserting at a new position, causing discomfort to the patient. The present invention eliminates this problem, instead keeping the penetrating member resident within the target site and using it as a channel for the transfer member to directly access the target site. Once inserted, material is injected through the transfer member and apertures at the distal end thereof. The transfer member may be pushed further through the penetrating member to reach a new area of the target site without adjusting the position of the penetrating member. Because the transfer member can slide freely within the penetrating member, longitudinal adjustments can be easily made to increase or decrease the amount or length of the transfer member extending beyond the end of the penetrating member. In addition to increasing

the target area axial to the penetrating member, a curved or flexible transfer member design allows for the radial target area to be increased. For example, one embodiment of the catheter comprises a 90 degree angle with a 2.8 cm bend radius. The transfer member may be made of a flexible material such as silicone so it can collapse or be temporarily deflected as it passes
5 into and through the penetrating member. Once the distal tip of the transfer member protrudes beyond the distal tip of the penetrating member, it may return to its natural shape and form, such as so that the distal tip is pointing at an angle (e.g. 90°) from the penetrating member axis. In some embodiments, a steerable guide wire is deployed down the lumen of the transfer member to provide structural support. When tension is applied to the guide member from the
10 distal end, the proximal tip of the transfer member deforms. With the transfer member pointing 90° from the penetrating member axis, cells that do not align with the penetrating member axis can be targeted. Being able to make these types of adjustments allows the healthcare practitioner to ensure the fluid is delivered or collected at a specific site. Increased accuracy may be useful for targeted delivery of therapeutic agents, such as chemotherapy drugs delivered specifically
15 to a tumor. Being able to deliver materials, such as fluids and therapeutics, directly to the desired target site allows for more efficient and specific treatment, which may reduce the amount of material needed overall, as well as reduce possible side effects from such materials. This may be particularly useful in the case of providing chemotherapy drugs or radioactive material, or other material that may have a negative effect on tissues other than the targeted
20 area. This may also be useful for delivering bone marrow from a donor directly to the recipient's bone marrow. This would eliminate the need to deliver HSCs via intravenous infusion, a process that is inefficient because many HSCs are lost in peripheral blood instead of reaching the bone marrow.

Equivalently, the medical device can also be used to extract or collect material from a
25 target site. The material collected may be solid tissue, fluid, suspension of cells or tissue in fluid, or other biological material in solid or liquid form, or any combination thereof. For instance, the device can be used to access bone marrow and collect samples of bone marrow for biopsy or harvesting. The device can be used to collect samples of any biological tissue, including soft materials such as bone marrow, and hard materials such as bone or bone lesions.
30 Accordingly, the device can be used to collect tissue samples for disease diagnosis and monitoring the progress or status of treatment of a disease through iterative biopsy. Such

diseases that can be diagnosed and monitored include, but are not limited to, cancers of all types, pre-cancerous states, diseases of the bone, blood disorders, including those that stem from bone marrow, and any disease or disorder in which biopsy can be useful for detection, diagnosis, confirmation, or monitoring. Materials may be collected through the transfer member. The transfer member includes a hub configured to interface with various components in fluid sealing engagement, such as a syringe. A healthcare practitioner would couple the syringe to the transfer member and create a vacuum to pull material through the apertures and transfer member and into the syringe.

Exemplary embodiments of the present invention also include a method for introducing hematopoietic stem cells into a patient, where the method comprises the following steps: (1) penetrating skin tissue with a penetrating member at a first skin penetration location; (2) penetrating bone tissue with the penetrating member at a first bone tissue penetration location; (3) inserting the penetrating member into bone marrow tissue proximal to the first bone tissue penetration location; and (4) injecting hematopoietic stem cells into the bone marrow tissue proximal to the first bone tissue penetration location.

Certain embodiments further comprise the following steps: (5) withdrawing the penetrating member from the bone marrow tissue, the bone tissue and the skin tissue; (6) penetrating the skin tissue with the penetrating member at a second skin penetration location; (7) penetrating bone tissue with the penetrating member at a second bone tissue penetration location; (8) inserting the penetrating member into bone marrow tissue proximal to the second bone tissue penetration location; and (9) injecting hematopoietic stem cells into the bone marrow tissue proximal to the second bone tissue penetration location.

Particular embodiments further comprise repeating steps (5) – (9) for a plurality of skin penetration locations and bone tissue penetration locations. In some embodiments, the penetrating member is a rigid cannula, and in specific embodiments, the penetrating member is a needle. In certain embodiments, the penetrating member comprises a first portion and a second portion configured to extend from the first portion. In some embodiments, the transfer member is equivalent to the second portion of the penetrating member. In specific embodiments, the second portion or transfer member comprises a plurality of apertures. Particular embodiments further comprise extending the second portion (or transfer member) from the first portion of the penetrating member after step (3) and before step (4). In some

embodiments, the first portion is rigid and the second portion is flexible, and in specific embodiments, the second portion is biodegradable.

Certain embodiments further comprise diffusing hematopoietic stem cells into the bone marrow over an extended period of time. In some embodiments, the extended period of time is greater than one day, or greater than one week, or greater than one month. Certain
5 embodiments further comprise injecting lentiviral particles into the bone tissue. In particular embodiments, the lentiviral particles are injected into the bone tissue prior to injecting hematopoietic stem cells into the bone tissue.

Exemplary embodiments include a method for introducing lentiviral particles into a
10 patient, where the method comprises the following steps: (1) penetrating skin tissue with a penetrating member at a first skin penetration location; (2) penetrating bone tissue with the penetrating member at a first bone tissue penetration location; (3) inserting the penetrating member into bone marrow tissue proximal to the first bone tissue penetration location; and (4)
15 injecting lentiviral particles into the bone marrow tissue proximal to the first bone tissue penetration location.

Certain embodiments further comprise the following steps: (5) withdrawing the penetrating member from the bone marrow tissue, the bone tissue and the skin tissue; (6) penetrating the skin tissue with the penetrating member at a second skin penetration location; (7) penetrating bone tissue with the penetrating member at a second bone tissue penetration
20 location; (8) inserting the penetrating member into bone marrow tissue proximal to the second bone tissue penetration location; and (9) injecting lentiviral particles into the bone marrow tissue proximal to the second bone tissue penetration location.

Particular embodiments further comprise repeating steps (5) – (9) for a plurality of skin penetration locations and bone tissue penetration locations. In some embodiments, the
25 penetrating member is a rigid cannula. In some embodiments, the penetrating member is a needle. In specific embodiments, the penetrating member comprises a first portion and a second portion (or transfer member) configured to extend from the first portion. Certain embodiments further comprise extending the second portion (or transfer member) from the first portion of the penetrating member after step (3) and before step (4). In particular
30 embodiments, the first portion is rigid and the second portion is flexible. In some

embodiments, the second portion is biodegradable. Specific embodiments further comprise diffusing hematopoietic stem cells into the bone marrow over an extended period of time.

In certain embodiments, the extended period of time is greater than one day, or greater than one week, or greater than one month. In particular embodiments, the second portion
5 comprises a plurality of apertures. Some embodiments further comprise injecting hematopoietic stem cells into the bone tissue. In specific embodiments the hematopoietic stem cells are injected into the bone tissue after injecting lentiviral particles into the bone tissue.

Further embodiments include a device configured to inject hematopoietic stem cells into a patient, where the device comprises: a reservoir comprising hematopoietic stem cells; a
10 penetrating member configured to penetrate bone tissue of the patient; and a transfer member selectively positionable through said penetrating member and in fluid communication with the reservoir. In certain embodiments, the penetrating member is a needle or cannula, and in some embodiments the penetrating member comprises a first portion and a second portion that is the transfer member and is configured to extend from the first portion. In some embodiments, the
15 first portion is rigid and the second portion (or transfer member) is flexible. In particular embodiments, the transfer member comprises a plurality of apertures. In specific embodiments, the transfer member is biodegradable.

Exemplary embodiments of the present disclosure include an actuated, mechanical system that will allow easy and rapid insertion of a penetrating member into the bone for
20 infusion of drugs or vectors for marrow transplantation and for gene therapy and related medical procedures. It is believed that such a needle would speed intraosseous (IO) needle insertion, allowing insertions into sites physically difficult to access with a manual needle. It is also believed that this system can be modified to allow a tubing to be placed through the actuated penetrating member to cover a greater area of intramedullary volume.

25 Cellular IO infusions for marrow transplantation and for gene therapy. Exemplary embodiments of the present disclosure comprise systems and methods for direct IO infusion of HSC in the bone marrow cavities. Marrow can be IO infused into one site, into multiple sites in one bone or in many bones to higher levels of chimerism or by an intraosseous tube, such as a transfer member, inserted through the penetrating member, infused over a wider
30 region of the marrow through a single or limited number of IO insertions. Such embodiments provide numerous advantages over existing IV infusion systems. For example, in exemplary

embodiments, less HSC will be required to repopulate the bone marrow, as many of the cells will be in the correct environment (HSC niche) to survive and proliferate. In general, this will reduce the requirement of HSC per transplant (autologous and allogeneic). Furthermore, exemplary embodiments of the present invention will increase the recovery of the patient, as
5 all (or nearly all) of the HSC will contribute to repopulate the hematopoietic system.

In addition, if partial allogeneic or transgenic chimerism is sufficient, then direct IO infusion may require less to no conditioning of the patients. Furthermore, as in gene therapy the HSCs need to be first transduced (genetically modified) before being infused into the patient. This can also reduce the number of corrected HSCs required, reducing the cost of
10 vector production.

Vector IO infusion for gene therapy. Using the actuated penetrating member, the direct IO infusion of gene therapy vectors into the marrow using an actuated penetrating member and delivery system is contemplated. Such an IO infusion using an actuated penetrating member will allow direct transfection of HSC in the marrow. The ability to infuse multiple sites in one
15 bone and to infuse multiple bones is made possible by the actuated penetrating member. The insertion of a transfer member using the inserted actuated penetrating member may allow even greater efficacy of HSC transfected. This strategy of IO injected vectors directly into the intramedullar space offers the advantage of not requiring marrow harvest or in vitro manipulation of the marrow. The actuated penetrating member allows one to achieve the
20 necessary level of marrow transfection for effective gene therapy.

In the present disclosure, the term “coupled” is defined as connected, although not necessarily directly, and not necessarily mechanically.

The use of the word “a” or “an” when used in conjunction with the term “comprising” in the claims and/or the specification may mean “one,” but it is also consistent with the
25 meaning of “one or more” or “at least one.” The term “about” means, in general, the stated value plus or minus 5%. The use of the term “or” in the claims is used to mean “and/or” unless explicitly indicated to refer to alternatives only or the alternative are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and “and/or.”

The terms “comprise” (and any form of comprise, such as “comprises” and
30 “comprising”), “have” (and any form of have, such as “has” and “having”), “include” (and any form of include, such as “includes” and “including”) and “contain” (and any form of contain,

such as “contains” and “containing”) are open-ended linking verbs. As a result, a method or device that “comprises,” “has,” “includes” or “contains” one or more steps or elements, possesses those one or more steps or elements, but is not limited to possessing only those one or more elements. Likewise, a step of a method or an element of a device that “comprises,”
5 “has,” “includes” or “contains” one or more features, possesses those one or more features, but is not limited to possessing only those one or more features. Furthermore, a device or structure that is configured in a certain way is configured in at least that way, but may also be configured in ways that are not listed.

Other objects, features and advantages of the present invention will become apparent
10 from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will be apparent to those skilled in the art from this detailed description.

DESCRIPTION OF THE DRAWINGS

Fig. 1 is a schematic diagram of one embodiment of an intraosseous access device of the present invention.

Fig. 2A is a schematic diagram of a penetrating member of the access device and system
20 of the present invention.

Fig. 2B is a cross-sectional view of the penetrating member of Figure 2A.

Fig. 2C is a schematic diagram of another embodiment of a penetrating member of the access device and system of the present invention, showing a side port.

Fig. 2D is a cross-sectional view of the penetrating member of Figure 2C.

Fig. 3 is a schematic diagram of the access device of Fig. 1 inserted into bone and accessing
25 an intraosseous space.

Fig. 4 is a schematic diagram of the access device of Fig. 1 where the penetrating member, reinforcing member and handpiece are decoupled.

Fig. 5 is a schematic diagram of one embodiment of a delivery system of the present invention, showing a penetrating member in an intraosseous space and a transfer member disposed
5 therethrough for intraosseous access.

Fig. 6A is a schematic diagram of one embodiment of a transfer member.

Fig. 6B is a cross-sectional view of the transfer member of Figure 6A.

Fig. 7A is a schematic diagram of the distal end of the transfer member.

Fig. 7B is a cross-sectional view of the distal end of the transfer member of Figure 7A.

Fig. 8 is a schematic diagram, partial cross-sectional view of the delivery of material
10 through the transfer member to a target site within an intraosseous space.

Fig. 9 is a schematic diagram of another embodiment of a delivery system of the present invention, including a guide member.

Fig. 10A is a schematic diagram of one embodiment of a guide member.

Fig. 10B is a cross-sectional view of the guide member of Figure 10A.
15

Fig. 11A is a cross-sectional view of a guide member positioned within a transfer member positioned within a penetrating member.

Fig. 11B is a zoomed in cross-sectional view of Figure 11A.

Fig. 12 is a schematic diagram of the delivery system of Figure 9, including a handpiece to
20 drive the guide member.

Fig. 13 is a schematic diagram of one embodiment of the system of the present invention, showing a reservoir of material for delivery or as collected from the target site.

Like reference numerals refer to like and corresponding parts throughout the Figures.

DETAILED DESCRIPTION

For purposes of describing relative configuration of various elements of the invention, the terms "distal", "distally", "proximal" or "proximally" are not defined so narrowly as to mean a particular direction, but, rather, are used as placeholders to define relative locations which shall be defined in context with the attached drawings and reference numerals. In addition, U.S. Patent No. 8,043,229 entitled "Medical Tool for Reduced Penetration Force," filed on June 27, 2008; U.S. Patent No. 8,328,738 entitled "Medical Tool for Reduced Penetration Force with Feedback Means," filed on September 14, 2009; U.S. Patent No. 9,220,483 entitled "Medical Tool with Electromechanical Control and Feedback," filed on February 10, 2012; U.S. Patent No. 8,777,871 entitled "Medical Tool for Reduced Penetration Force with Feedback Means," filed on November 8, 2012; U.S. Patent Application Serial No. 14/329,177 entitled "Medical Tool for Reduced Penetration Force with Feedback Means," filed on July 11, 2014; U.S. Patent Application Serial No. 14/522,681 entitled "Device and Method for Less Forceful Tissue Puncture," filed on October 24, 2014; U.S. Patent Application Serial No. 14/689,982 entitled "Medical Tool for Reduced Penetration Force," filed on April 17, 2015; and U.S. Patent Application Serial No. 14/976,939 entitled "Medical Tool with Electromechanical Control and Feedback," filed on December 21, 2015 are all incorporated by reference herein in their entireties.

The present invention is directed to systems and methods for access to, delivery to and collection of materials from a target site within biological tissue, preferably living intraosseous tissue. As specifically seen in FIGURE 1, the system of the present invention includes an access device 100 configured to penetrate bone and gain access to an intraosseous space. The access device 100 includes a penetrating member 110, preferably having an elongate, tubular configuration with a hollow interior. Examples of a penetrating member 110 include, but are not limited to, a cannula or needle. As seen in Figures 1-2B, the penetrating member 110 includes at least one wall that defines the hollow penetrating member lumen 114 therein. This wall may be made of any material appropriate for use in medical devices, including but not limited to metals, such as stainless steel 316, 316L, and 304, hard and soft plastics, polymer-based materials, inert material, acetal, polyethylene, polycarbonate, PEEK, Ultem PEI, polypropylene, polysulfone and polyurethane. The penetrating member 110 may be made of a single type of material throughout, or comprise a plurality of different materials, in any

combination or configuration along its length. In some embodiments, the penetrating member 110 may comprise concentric layers of different materials, such as an outer layer of 316L stainless steel for better structural integrity, biocompatibility, and corrosion resistance with an interior concentric layer of copper. The purpose of the copper layer is to provide a means of heat transfer from the friction generated between the outer stainless steel layer and the penetrated tissue.

In addition, the penetrating member 110 may be straight in at least one embodiment. In other embodiments, the penetrating member 110 may be at least partially curved along a portion of its length. The curvature may comprise arcuate curves and angular changes in direction, which can redirect the penetrating member 110 in any three-dimensional direction. Accordingly, the curvature may be of any angle or curve from zero to 360 degrees, thereby including both acute and oblique angles. For instance, the penetrating member 110 may have an angle from 0° to 180° and a bend radius from 2 cm to 4 cm, more optimally an angle of 90° with a bend radius of 2.8 cm. Further, some embodiments contemplate a penetrating member 110 having sections, wherein some sections are straight and other sections are curved. For instance, in some embodiments, the distal end of the penetrating member 110 may be curved, such as over a length of 1 - 5 cm from the distal tip 112, and preferably 2.8 cm therefrom, with the remainder of the penetrating member 110 being straight. Any combination of straight and curved sections is contemplated herein.

The penetrating member 110 also includes a distal tip 112 located opposite the handpiece 50, as shown in FIGURES 1 – 2B. The distal tip 112 is advanced into the tissue during use of the device that leads the penetration into the tissue, and includes an opening at the distal tip 112. In some embodiments, the distal tip 112 is sharp for piercing tissue, and may have any suitable configuration, including but not limited to tri-tip, saw tooth and beveled edge configurations. Further, in at least one embodiment, the distal tip 112 includes at least one sharpened edge, sharp facet such as a trocar, bevels, or any combination of features and configurations permitting penetration of tissues, which may be soft tissues such as skin, venous material and bone marrow, or harder tissue such as tendon or bone. The tissues are preferably biological tissues, and may be living or dead at the time of penetration. Further, the tissues may be attached to the host at the time of penetration, delivery and/or extraction by the system, and may therefore be considered in vivo, or may be ex vivo tissues previously excised or

extracted from a subject. In some embodiments, the distal tip 112 may be dull or blunt, such as but not limited to atraumatic and pencil point tips, to reduce damage to tissues as the penetrating member 110 is inserted.

5 In addition to a distal tip 112, the penetrating member 110 also has an opposite proximal end. The penetrating member lumen 114 extends through the length of the penetrating member 110 and both the proximal and distal ends. The penetrating member 110 includes a penetrating member hub 118, as seen in FIGURES 1 – 2B. The penetrating member hub 118 is sized and shaped to transition between the elongated tube of the penetrating member 110 and another component of the device, such as a handpiece 50, or other devices or accessories, such as
10 syringes, stylets, collection devices, ablation devices, etc. The penetrating member hub 118 may be made of any appropriate material(s), including metals such as stainless steel, titanium, plated brass, and aluminum, plastics such as polyvinyl chloride (PVC), acrylonitrile butadiene styrene (ABS), polyethylenes and polycarbonates, polymeric compounds, and inert materials. These materials are provided for illustrative purposes and are not intended to be limiting or an
15 exhaustive list of possible materials.

The penetrating member hub 118 is configured to interface with various components in fluid sealing engagement, such as with a syringe, infusion pump, stylet, collection device, handpiece, etc. This interface mechanism may be located opposite the proximal end of the penetrating member 110. The interface mechanism of the penetrating member hub 118 may
20 be any configuration capable of fluid sealing engagement, such as but not limited to Luer-type fittings, tapers, threading, sliding, locking, and other structures suitable for selective engagement and disengagement. In a preferred embodiment, the penetrating member hub 118 is selectively attachable to an interfaced component, such as a handpiece 50 to receive oscillating vibrations, as described in greater detail below. The penetrating member hub 118
25 may also be selectively attachable to another interfaced component such as a syringe, stylet, aspirator to enable fluid sealing engagement when desired, such as for material delivery or aspiration. The penetrating member hub 118 can also be released and removed from the handpiece 50 or other interfaced component when desired, such as when the relevant part of the procedure has been completed.

30 In some embodiments, the penetrating member hub 118 includes a channel 119 extending from the proximal end of the penetrating member 110 through the penetrating

member hub 118. Such channel 119 is aligned with and forms a continuous bore with the penetrating member lumen 114 through fluid-tight mechanical coupling, as depicted in FIGURE 2B. This channel 119 therefore permits the delivery or removal of materials such as biological tissue, stem cells, HSCs, gene therapies, therapeutic agents, drugs, saline, and other materials through the penetrating member hub 118. The penetrating member hub 118 may connect to the proximal end of the penetrating member 110 by secure, fluid sealing connection, such as but not limited to press-fit, brazing, soldering, molding, overmolding, snap-fitting, swaging or other common plastic-plastic, metal-metal, or plastic-metal connection forming techniques.

In at least one embodiment, as shown in FIGURES 2C and 2D, the penetrating member hub 118 may also include an auxiliary port(s) 117 to permit access for the introduction of auxiliary material such as saline used for cooling. The auxiliary port(s) 117 may preferably be located on the side of the penetrating member hub 118 to access the channel 119 of the penetrating member hub 118 from the side, such as at an angle. The angle of access or approach may be any angle between zero and 180° relative to the axis of the channel 119, and may be at a 90° angle or oblique angle relative thereto.

In some embodiments, the penetrating member 110 may be made of, or the penetrating member lumen 114 lined with, certain material(s) to increase or decrease thermal conductivity of the penetrating member 110, as may be needed. For example, the heat generated by the insertion process or repetitive motion of the penetrating member 110, described in greater detail hereinafter, could potentially damage the integrity of the tissue or material being delivered or sampled. The heat should therefore be drawn away from the tissue or target site, to avoid damage or deleterious effect. Integrating higher thermal conductivity metals such as copper or thermal paste with the penetrating member 110 may act as a heat sink and help to remove heat from the distal tip 112 more effectively. Thermally insulating materials such as an air gap or insulating rubber may also be used to protect the delivery materials or samples from heat. In some embodiments, a combination of thermally conductive materials and thermally insulating materials may be used collectively to protect the material or sample. A combination of materials with different thermal conductivity may be used to provide selective heat transfer from specific surfaces, such as the penetrating member distal tip 112, to other surfaces such as a Peltier cooler, thermoelectric cooler, or passive or active heat sink. In other

examples, a temperature measuring component such as a thermocouple may be integrated into the interior or exterior of the penetrating member 110 or into the interior or exterior of the transfer member 230. For example, the penetrating member 110 may comprise an outer stainless steel layer and an inner copper layer used to provide heat transfer from the friction
5 generated between the outer stainless steel layer and the penetrated tissue.

In certain embodiments, the access device 100 of the system 200 also includes a reinforcing member 120 such as a stylet, as seen in FIGURES 1, 3 and 4. The reinforcing member 120 is removably and selectively positionable within at least a portion of the penetrating member lumen 114, and provides mechanical rigidity to the penetrating member
10 110 during insertion and/or removal. Accordingly, the reinforcing member 120 may be inserted coaxially into the penetrating member lumen 114 for at least a portion of the insertion process.

The reinforcing member may also prevent biological tissue from entering the penetrating member lumen 114 during insertion to the target site. For instance, when the reinforcing member 120 is fully disposed within the entire length of the penetrating member
15 110, as in FIGURE 1, the reinforcing member 120 blocks the opening at the distal tip 112. In at least one embodiment, as shown in FIGURE 1, a reinforcing member tip 124 extends at least partially through the opening of the distal tip 112 of the penetrating member 110. Therefore, biological material may not enter the penetrating member 110 during the insertion process.
20 When delivery of material is desired, the reinforcing member 120 may be removed from the penetrating member 110, as shown in FIGURE 3. This unblocks the opening at the distal tip 112 of the penetrating member 110 and permits the delivery of material through the penetrating member lumen 114 to and from the target site.

The reinforcing member 120 may be made of any suitable material as may confer
25 mechanical rigidity. For example, the reinforcing member 120 may be made of metal such as stainless steel 316, 316L, and 304, titanium, or aluminum, ceramic, hard plastic, and composites of various materials. In some embodiments, the reinforcing member 120 is made of thermal conductive material such as copper, so as to act as a thermal wick or heat sink when inserted into the penetrating member 110, drawing heat away from the biological tissue and
30 the penetrating member 110.

The reinforcing member 120 may comprise any suitable shape. For instance, in a preferred embodiment, the reinforcing member 120 has an elongate length and a radius of sufficient size to fit coaxially within the penetrating member lumen 114. In some embodiments, the reinforcing member 120 and penetrating member 110 fit tightly together, such as when thermal conduction is beneficial. In other embodiments, the radius of the reinforcing member 120 is less than that of the penetrating member lumen 114 such that the reinforcing member 120 may or may not contact the interior wall of the penetrating member 110. Further, the reinforcing member 120 comprises a distal end terminating in a reinforcing member tip 124, which is inserted into the proximal end of the penetrating member 110. The reinforcing member tip 124 is preferably sharp, such as to aid in cutting through the tissue, and may have a trocar shape or similar structure.

In certain embodiments, the reinforcing member 120 may also include a reinforcing member hub 128 at a proximal end thereof, as shown in FIGURES 3 and 4. The reinforcing member hub 128 is sized and shaped to transition between the diameter of the reinforcing member 120 and the handpiece 50. The reinforcing member hub 128 may be made of any appropriate material(s), including metals such as stainless steel, titanium, and aluminum, plastics such as polyvinyl chloride (PVC), acrylonitrile butadiene styrene (ABS), polyethylenes and polycarbonates, polymeric compounds, and inert materials. These materials are provided for illustrative purposes and are not intended to be limiting or an exhaustive list of possible materials.

The reinforcing member hub 128 includes an interface mechanism opposite the proximal end of the reinforcing member 120 for selective attachment to and detachment from the handpiece 50. The interface mechanism may be any configuration capable of securely and reversibly attaching to the handpiece 50, such as Luer-type fittings, tapers, threading, sliding, locking, and other structures suitable for selective engagement and disengagement. In a preferred embodiment, the reinforcing member hub 128 is selectively releasable from the handpiece 50, so as to enable the handpiece 50 to connect to other components of the system, such as the penetrating member 110.

As seen in FIGURE 1, the access device 100 also includes at least one handpiece 50 that may be gripped by a user for placing, guiding and using the penetrating member 110 and reinforcing member 120 to pierce bone and access the intraosseous space or the space beyond

the bone. The handpiece 50 has a body which is ergonomically shaped to be held by a user of the device during use. The handpiece 50 may include a connection point 55, as seen in FIGURE 4, to selectively engage and disengage with the penetrating member hub 118, reinforcing member hub 128, transfer member hub 238, guide member hub 248, or other medical device, such as a syringe, infusion pump, material reservoir or aspirator.

The handpiece 50 includes at least one driving actuator 51, depicted schematically in FIGURE 1, which may be a piezoelectric, electromagnetic, solenoid, pneumatic, fluidic or any oscillatory, translational and/or rotational actuator. In at least one embodiment, different handpieces 50 are included in the system 200, and each handpiece 50 may include a different type of driving actuator (such as piezoelectric, electromagnetic, solenoid, pneumatic, fluidic or any oscillatory, translational and/or rotational actuator) configured to provide a different type of oscillatory motion (such as linear, axial, longitudinal, rotational). Moreover, different driving actuators 51 and/or handpieces 50 may be used in the system 200 depending on the particular tissue being penetrated. The driving actuator(s) 51 imparts a repetitive oscillatory motion that may be continuous or discontinuous including but not limited to longitudinal and transverse oscillation, or rotation to the penetrating member 110, utilizing a reduction of force to optimize penetration through biological tissues found within the body, such as bone, muscle, fat, skin, and tendon. Essentially, when tissue is penetrated by the penetrating member oscillating at a frequency between 1 Hz - 80 kHz, and more preferably 20 - 60 kHz the force required for entry is reduced. In other words, a reduction of force effect is observed when the penetrating member 110 or other component receiving oscillatory vibration during the insertion process and enough mechanical energy is present to break adhesive bonds between tissue and the penetrating member 110. The threshold limits of energy for any type of driving actuator(s) 51 can be reached in the sonic to ultrasonic frequency ranges if the necessary amount of penetrating member displacement is present, such as in the range of 0.1 to 100 μm .

In at least one embodiment, the driving actuator 51 may be a flextensional actuator. Flextensional actuator assembly designs have been developed which provide amplification in piezoelectric material stack strain displacement. The flextensional designs comprise a piezoelectric material driving cell disposed within a frame, platen, endcaps or housing. The geometry of the frame, platten, endcaps or housing provides amplification of the axial or longitudinal motions of the driver cell to obtain a larger displacement of the flextensional

assembly in a particular direction. Essentially, the flextensional actuator assembly more efficiently converts strain in one direction into movement or force in a second direction. Flextensional piezoelectric actuators may be considered mid-frequency actuators, and may operate in the range of 25-35kHz. Flextensional actuators may take on several embodiments.

5 For example, in one embodiment, flextensional actuators are of the cymbal type, as described in United States Patent No. 5,729,077 (Newnham), which is hereby incorporated by reference. In another embodiment, flextensional actuators are of the amplified piezoelectric actuator (“APA”) type as described in U.S. Patent No. 6,465,936 (Knowles), which is hereby incorporated by reference. The flextensional actuator assembly provides for improved

10 amplification and improved performance, which are above that of a conventional handheld device. For example, the amplification may be improved by up to about 50-fold. Additionally, the flextensional actuator assembly enables handpiece configurations to have a more simplified design and a smaller format in comparison to other commonly used actuator designs. In yet another embodiment, the actuator is a Langevin or bolted dumbbell-type actuator, similar to,

15 but not limited to that which is disclosed in U.S. Patent Application Publication No. 2007/0063618 A1 (Bromfield), which is hereby incorporated by reference.

The driving actuator 51 is in electrical communication with a power source, such as by connection through a power cord 54 shown in FIGURE 1. The power source may be AC power, DC power, battery power, or other source of electrical stimulation. In some

20 embodiments, the power source 54 may be internally housed within the handpiece 50, as in the case of a locally housed battery. In at least one embodiment, the handpiece 50 may further include an inverter, such as an oscillator/amplifier, etc., in electrical communication between the power source and the driving actuator 51. Upon receiving an electrical signal, the driving actuator 51 converts the electrical energy into mechanical energy that is transmitted to the

25 penetrating member 110. In the case of a Langevin actuator, the vibratory motion produced by the piezoelectric materials generates a standing wave through the whole assembly.

In at least one embodiment, the driving actuator 51 includes at least one piezoelectric element. Piezoelectric elements, such as each of one or more piezoelectric material rings are capable of precise, controlled displacement and can generate energy at a specific frequency.

30 The piezoelectric materials expand when exposed to an electrical input, due to the asymmetry of the crystal structure, in a process known as the converse piezoelectric effect. Contraction is

also possible with negative voltage. Piezoelectric strain is quantified through the piezoelectric coefficients d_{33} , d_{31} , and d_{15} , multiplied by the electric field, E , to determine the strain, x , induced in the material. Ferroelectric polycrystalline materials, such as barium titanate (BT) and lead zirconate titanate (PZT), exhibit piezoelectricity when electrically poled. Simple devices composed of a disk or a multilayer type directly use the strain induced in a material by the applied electric field. Acoustic and ultrasonic vibrations can be generated by an alternating field tuned at the mechanical resonance frequency of a piezoelectric device. Piezoelectric components can be fabricated in a wide range of shapes and sizes. In one embodiment, piezoelectric component may be 2-5mm in diameter and 3-5mm long, possibly composed of several stacked rings, disks or plates. The exact dimensions of the piezoelectric component are performance dependent. The piezoelectric single or polycrystalline materials may be comprised of at least one of lead zirconate titanate (PZT), multilayer PZT, lead magnesium niobate-lead titanate (PMN-PT), multilayer PMN-PT, lead zinc niobate-lead titanate (PZN-PT), polyvinylidene difluoride (PVDF), multilayer PVDF, and other ferroelectric polymers. These materials also can be doped which changes properties and enhances the performance of the medical device. This list is not intended to be all inclusive of all possible piezoelectric materials, which may also contain non-lead (Pb) containing materials, for example. Additional details of the driving actuator may be found in U.S. Patent No. 9,220,483 (Frankhouser), which is incorporated by reference herein.

In some embodiments, the system 200 may include a feedback process, providing a visual, audible, and/or tactile response, using a variety of detection mechanisms (such as, but not limited to, electrical, magnetic, pressure, capacitive, inductive, etc.), to indicate successful penetration of various tissues, such as cortical bone or bone marrow, or voids within the body such as the intraosseous space, so that the healthcare practitioner may discern where to navigate the penetrating member 110 and when to stop, as well as to limit power to the driving mechanism. Further details of the feedback process may be found in U.S. Patent No. 9,220,483 (Frankhouser) and U.S. Patent Application Publication No. 2014/0323855 (Frankhouser), the entire contents of both of which are incorporated by reference.

Driving actuators 51 of the various embodiments may produce displacements between 2 μm -10 mm. To exploit the reduction of force effect, at least one embodiment of the access device 100 is designed such that the distal tip 112 of the penetrating member 110 attains a

short travel distance or displacement, and vibrates sinusoidally with a high penetrating frequency. The sinusoidal motion of the sharp distal tip 112 may include a displacement for piezoelectric tools of between 0.1 μm – 30 mm at a frequency of between 1 Hz - 80 kHz. In one embodiment, the oscillation would be driven by a piezoelectric tool, most preferably at 22-38 kHz with a displacement of 2-100 μm . This motion is caused by the penetrating member 110 being attached to an actuating piezoelectric actuator operated at 50-150 Vpp/mm, but most preferably at 60-90 Vpp/mm where Vpp is known at peak-to-peak voltage. In another embodiment, the oscillation would be driven by an electromagnetic motor, operated at a frequency of 20 – 200 Hz with a displacement of 0.1 mm to 30 mm. Further details of the parameters of reciprocating movement are described in U.S. Patent Nos. 8,043,229 (Mulvihill) and 8,328,738 (Frankhouser), the contents of both of which are incorporated by reference herein in their entirety.

The handpiece 50 may also include a motor shaft 52 extending between the driving actuator 51 and the connection point 55, as shown in FIGURE 1. The motor shaft 52 is a rigid structure that connects the connection point 55 and driving actuator 51 such that the axially oscillating vibrations generated by the driving actuator 51 are transmitted to the component attaching to the handpiece 50 at the connection point 55, such as the penetrating member 110, reinforcing member 120, transfer member or guide member 240 through their respective hubs 118, 128, 238 or 248.

In at least one embodiment, the handpiece 50 may selectively engage and disengage the penetrating member hub 118, reinforcing member hub 128, transfer member hub 238, and/or guide member hub 248. For instance, in the embodiment of FIGURES 1 and 3, the reinforcing member hub 128 may be connected to the handpiece 50 for use in penetrating tissue. Once the bone is penetrated, as in FIGURES 3 and 4, the reinforcing member hub 128 may be selectively disengaged from the handpiece 50, allowing the penetrating member hub 118 or other component to connect to the handpiece 50. Subsequently, the penetrating member 110 may be vibrated by the handpiece 50 and inserted further in order to obtain a tissue sample. After the sample has been collected, the penetrating member 110 is removed from the patient and disengaged from the handpiece 50 to allow the sample to be removed from the penetrating member 110.

In another embodiment, the penetrating member hub 118 may be connected to the handpiece 50 for use in penetrating tissue. Once penetrated, the penetrating member hub 118 may be selectively disengaged from the handpiece 50, allowing the transfer member hub 238 or guide member hub 248 to engage with the handpiece, as in FIGURE 12. The handpiece 50 may then be used to penetrate the transfer member 230 deeper into the tissue. Subsequently, the transfer member hub 238 or guide member hub 248 may then be selectively disengaged from the handpiece 50 to engage with a syringe or reservoir 250 for the introduction of material into the penetrating member 110, and subsequently the target site 3, as in FIGURE 13 and described in greater detail hereinafter. Subsequently, the syringe or reservoir 250 may be disengaged and the handpiece 50 reengaged by the penetrating member hub 118 for the removal of the penetrating member 110 by reduced force.

In another embodiment, the handpiece 50 and penetrating member hub 118 may remain mechanically coupled, and a syringe or reservoir 250 of material may be connected to the handpiece 50 in fluid communication therewith. In this embodiment, the handpiece 50 may include a channel extending through the body of the handpiece 50 to align with and form a continuous bore with the channel 119 of the penetrating member hub 118, and therefore with the penetrating member lumen 114. Here, a syringe or other material reservoir 250 may be attached to the handpiece 50 at the channel end opposite of the penetrating member hub 118 to permit introduction or removal of material. Similarly, the reinforcing member 120 may be inserted and removed from the medical device through such a channel in the handpiece 50. Other implements can also be inserted through the handpiece channel to access the distal end of the penetrating member 110, such as implements for tissue manipulation, aspiration and cryofreezing to name a few. Further, the handpiece 50 may be sterilizable using such methods as steam sterilization, a sleeve, UV radiation, and ethylene oxide (ETO).

To pierce the bone and gain access to the intraosseous space, the penetrating member 110 may first be coupled to the reinforcing member 120 such that it sits coaxially and fully within the length of the penetrating member 110, as shown in FIGURE 1. The reinforcing member 120 may then be coupled to the handpiece 50. In some embodiments, however, the penetrating member 110 may be directly coupled to the handpiece 50, and no reinforcing member 120 is needed. For insertion, the healthcare practitioner may use a scalpel to perform an initial incision through the skin and any muscle tissue on top of the bone insertion site,

although in some embodiments, the penetrating member 110 may be used to pierce through the skin, muscles, tendons, ligaments, or other soft tissue between the skin and bone. The distal tip 112 of the penetrating member 110 is brought to the insertion site, and may be aligned at an angle of insertion relative to the skin 5, bone 7 or other surface of entry. The angle of insertion may be any angle, and includes oblique angles. In at least one embodiment, the angle of insertion is in the range of 10° to 90° relative to the entry surface, such as the skin 5 or bone 7. The driving actuator 51 is activated such that the distal tips 112, 124 of the penetrating member 110 and/or reinforcing member 120 are axially oscillated.

As the penetrating member 110 and/or reinforcing member 120 oscillate against bone, tissue bonds are broken. The healthcare practitioner may twist the handpiece 50, such as clockwise between 0 and 360 degrees but more preferably by at least 60 degrees and then counterclockwise between 0 and 360 degrees but more preferably by at least 60 degrees to clear resulting fragments of bone. The removal of tissue in front of the penetrating member 110 path reduces the force necessary to advance the penetrating member 110, allowing the distal tip 112 to pierce and anchor into bone, even at oblique insertion angles. A slight force, such as around 18 N, may be applied to advance the penetrating member 110 through the bone, such as cortical bone. The penetrating member is then advanced through the outer layer of bone until the desired position within the target is reached. The desired position may be defined when the distal tip 112 of the penetrating member 110 reaches and/or contacts the target area or tissue for delivery. For example, in the embodiment of FIGURE 3, the target site is bone marrow 9. The penetrating member 110 is advanced through the skin 5, muscle and other tissue, and through the cortical bone 7, and finally into the bone marrow 9. Aided by the depth markings on the penetrating member 110, imaging and/or tactile feel, the healthcare practitioner halts forward movement of the penetrating member 110 when the target site has been reached.

At this point, the driving actuator 51 may be deactivated, the penetrating member 110 decoupled from the reinforcing member 120 or handpiece 50, depending on whether a reinforcing member 120 is used, and the reinforcing member 120 may be decoupled from the handpiece 50, such as at FIGURE 4. The penetrating member 110 remains in the target site. With this access channel in place, materials may be delivered to or extracted from target sites.

In at least one embodiment, as shown in FIGURE 5, the system 200 also includes a transfer member 230 that is selectively and adjustably positionable through the penetrating member lumen 114 to access the target site and improve accuracy of material delivery and extraction. The transfer member 230 may be coaxially positioned in the penetrating member lumen 114 and may be selectively movable therethrough independently of the penetrating member 110, such that the penetrating member 110 remains in place within the target site 3 and the transfer member 230 may be extended further into, maneuvered around within, and retracted from the target site 3 without affecting the penetrating member 110 placement. The transfer member 230 may be made out of any appropriate material(s), including but not limited to metals such as nitinol, stainless steel, titanium, and aluminum, plastics such as polyvinyl chloride (PVC), acrylonitrile butadiene styrene (ABS), silicone, PVC, ethyl vinyl acetate, polyurethane, thermoplastic elastomers, polyethylenes and polycarbonates, polymeric compounds, and inert materials. In one embodiment, the transfer member 230 is made of a material of a sufficient hardness to penetrate bone marrow without deflecting or breaking, such as a plastic with a shore hardness of 75A-80D. In another embodiment, the transfer member 230 has a flexible material so that a permanently curved transfer member 230 could squeeze through the straight penetrating member 110, such as a plastic with a shore hardness of 30A-70A on the shore A scale. The transfer member 230 may comprise segments made out of different materials, with differing levels of hardness and flexibility. For example, the transfer member 230 may have a flexible, curved portion followed by a rigid, straight portion that helps to push the flexible portion within the penetrating member 110. In another embodiment, the transfer member 230 has a flexible material, such as a plastic with a shore hardness of 60A-90D or another deformable material such as nitinol, so that a permanently curved transfer member 230 can be temporarily deflected to pass through the straight penetrating member 110 and resume its preformed shape once beyond the distal tip 112 of the penetrating member 110. In another embodiment, the transfer member 230 may have flexible portions comprised of segments with flexible material, such as a plastic with a shore hardness of 20A-70A.

In some embodiments, the transfer member 230 may be straight. In other embodiments, the transfer member 230 is at least partially curved. The curvature may comprise arcuate curves and angular changes in direction, which can redirect the transfer member 230 in any three-dimensional direction. Accordingly, the curvature may be of any angle or curve from

zero to 360 degrees, thereby including both acute and oblique angles. Embodiments could have an angle from 0° to 180° and a bend radius from 2 cm to 4 cm, more optimally an angle of 90° with a bend radius of 2.8 cm. For instance, in some embodiments as in FIGURES 7A and 7B, the distal end 232 of the transfer member 230 may be curved, such as over a length of about 0.1 to 5 cm from the distal tip, and more preferably about 2.8 cm, with the remainder of the transfer member 230 being straight. Any combination of straight and curved sections is contemplated herein.

In some embodiments, the transfer member 230 may contain a section of material that is radio opaque for improved visibility under radiographic imaging, such as x-ray or computer tomography (CT) imaging. The section of radio opaque material may be integrated into the distal tip of the transfer member or be dispersed throughout.

As seen in FIGURE 6A, the transfer member 230 may include one or multiple markings 233 on the exterior of the wall. These markings 233 may be used to indicate depth, to provide the user of the system 200 with an understanding of how far into the patient or tissue, or even which tissue, the transfer member 230 has reached. Such markings 233 therefore assist in the insertion and removal of the transfer 230 member from a subject, as well as sample collection and delivery of materials to a target site.

In some embodiments, the transfer member 230 has a distal end 232 and a plurality of apertures 235 extending through the wall of the transfer member 230, as shown in FIGURES 6A – 7B. The apertures 235 may be located anywhere along the length of the transfer member 230, though preferably are included at least at the distal end 232 of the transfer member 230. In some embodiments, apertures 235 may be located only in the middle of the transfer member 230, or in both the middle and distal ends of the transfer member 230. In one embodiment, apertures 235 may be located along the entire length of the transfer member 230. In other embodiments, apertures 235 may be located at any portion(s) of the transfer member 230. Moreover, the apertures 235 may be arranged circumferentially around the transfer member 230, or along a line(s) extending longitudinally at least a portion of the length of the transfer member 230, and in any pattern, spacing and configuration therealong. Some embodiments include apertures 235 disposed both circumferentially and longitudinally along the transfer member 230.

The apertures 235 may be of any size and configuration to permit the movement of materials such as bone marrow, blood, cells, stem cells, HSCs, gene therapies, viruses, vectors, lentiviral vectors, DNA, RNA, proteins, peptides, antibodies, medications, therapeutics, and other materials therethrough. The presence of the apertures 235 in the transfer member 230 provide a number of openings, thereby assisting in the delivery and extraction of materials to and from the target site. For instance, the apertures 235 increase the transfer rate of fluid out of the transfer member 230 as needed for delivery of materials to the target area, as well as into the transfer member 230 for the extraction/aspiration of materials from the target area. Moreover, the increase in fluid and material transfer rate increases with the size of each aperture 235 and number of apertures 235 available to the target site. For similar reasons, the apertures 235 also assist in diffusion of materials into the target site from the transfer member 230 (during delivery) and into the transfer member 230 from the target site (during extraction). FIGURE 8 shows one example where the transfer member 230 is inserted through skin 5, cortical bone 7, and into bone marrow 9. The apertures 235 increase the delivery/extraction area of the transfer member 230 to include those areas where the apertures 235 are located. In the example of FIGURE 8, material 20 may be provided and inserted through the transfer member 230 in a direction 22 toward the target site 3, and specifically the bone marrow 9. When the apertures 235 are reached, the material 20 flows out the apertures 235 and into the surrounding target site 3. Although delivery of material 20 is depicted in FIGURE 8, it should be understood and appreciated that extraction or collection of material 20 from the target site 3 through the apertures 235 and transfer member 230 in a direction opposite of direction 22 is contemplated for extraction or collection. Examples of material 20 that can be delivered or collected include, but are not limited to, stem cells, modified stem cells, hematopoietic stem cells, DNA modifying vectors, viruses, viral vectors, lentiviral vectors, lentiviral particles, DNA, DNA complexes, RNA, RNA complexes, proteins, peptides, antibodies virosomes, gene therapies, drugs, medicines, therapeutic materials, blood, and bone marrow.

As seen in FIGURES 6A and 6B, in addition to a distal end 232, the transfer member 230 also has an opposite proximal end 244 and a transfer member lumen 234 extending therebetween. The transfer member lumen 234 extends through the length of the transfer member 230 and is in fluid communication with the apertures 235. The proximal end 244 includes a transfer member hub 238, which is sized and shaped to transition between the

transfer member 230 and another component of the device or system, such as a handpiece 50, or other devices or accessories, such as syringes, stylets, collection devices, and ablation devices to name a few examples. The transfer member hub 238 may be made of any appropriate material(s), including metals such as stainless steel, titanium, and aluminum, plastics such as polyvinyl chloride (PVC), acrylonitrile butadiene styrene (ABS), polyethylenes and polycarbonates, polymeric compounds, and inert materials. These materials are provided for illustrative purposes and are not intended to be limiting or an exhaustive list of possible materials.

The transfer member hub 238 is configured to interface with various components in fluid sealing engagement, such as with a syringe, stylet, collection device, handpiece 50, etc. Accordingly, interface mechanism may be located opposite the proximal end of the transfer member 230. The interface mechanism may be any configuration capable of fluid sealing engagement, such as Luer-type fittings, tapers, threading, sliding, locking, and other structures suitable for selective engagement and disengagement. In a preferred embodiment, the transfer member hub 238 is selectively releasable from the interfaced component, such as a handpiece 50, syringe, stylet, aspirator, or others so as to enable fluid sealing engagement when desired such as when during fluid delivery or aspiration. The transfer member hub 238 can also be released and removed when desired, such as when the procedure has been completed.

In at least one embodiment, the transfer member hub 238 includes a channel 239 extending from the proximal end 244 of the transfer member 230 to the opposite end of the transfer member hub 238. Such channel 239 is aligned with and forms a continuous bore with the transfer member lumen 234 through fluid-tight mechanical coupling. This channel 239 therefore permits the delivery or removal of materials such as blood, bone marrow, cells, stem cells, HSCs, viruses, lentiviral vectors, DNA, RNA, proteins, peptides, antibodies, gene therapies, biological tissue, therapeutic agents, drugs, saline, and other materials through the transfer member hub 238. The transfer member hub 238 may connect to the proximal end 244 of the transfer member 230 by secure, fluid sealing connection, such as but not limited to press-fit, brazing, soldering, molding, overmolding, snap-fitting, swaging or other common plastic-plastic, metal-metal, or plastic-metal connection forming techniques.

In some embodiments, such as where the transfer member 230 must be flexible yet still penetrate tough tissue such as the spongy bone where marrow resides, a guide member 240

may be employed to provide rigidity to the transfer member 230, as seen in FIGURE 9. The guide member 240 may be inserted into the transfer member lumen 234 either before or during insertion of the transfer member 230 into or through the penetrating member 110, as shown in FIGURES 11A and 11B. The guide member 240 may be of a harder or more rigid material to provide support to the transfer member 230 during insertion and/or removal. Once the transfer member 230 is in place at the target site 3, the guide member 240 may be removed so materials 20 may be delivered or collected through the transfer member 230.

The guide member 240 may be made of any appropriate material(s), including metals such as nitinol, stainless steel, titanium, and aluminum, plastics such as nylon PA, polyvinyl chloride (PVC), acrylonitrile butadiene styrene (ABS), polyethylenes and polycarbonates, polymeric compounds, and inert materials. These materials are provided for illustrative purposes and are not intended to be limiting or an exhaustive list of possible materials. In one embodiment, the guide member 240 material is of sufficient stiffness to allow the transfer member 230 to cut through the bone marrow and/or surrounding cancellous bone. The guide member 240 may comprise segments made out of different materials, which may have different levels of rigidity.

In some embodiments, as depicted in FIGURES 10A and 10B, the guide member 240 is solid and does not have an internal lumen. The tip of the guide member 240 at a distal end 242 is blunt so as not to damage the distal end 232 of the transfer member 230 when inserted therein. In addition, the guide member 240 may be straight or at least partially curved. The curvature may comprise arcuate curves and angular changes in direction, which can redirect the guide member 240 in any three-dimensional direction. Accordingly, the curvature may be of any angle or curve from zero to 360 degrees, thereby including both acute and oblique angles. Embodiments could have an angle from zero to 180 degrees and a bend radius from 2 cm to 4 cm, more optimally an angle of 90 degrees with a bend radius of 2.8 cm. Further, some embodiments contemplate a guide member 240 having sections, wherein some sections are straight and other sections are curved. For instance, in some embodiments, the distal end 242 of the guide member 240 may be curved, such as over a length of 2.8 cm from the distal tip, and the remainder of the guide member 240 is straight. Any combination of straight and curved sections is contemplated herein.

The guide member 240 also includes a proximal end 244 opposite the distal end 242. The proximal end 244 includes a guide member hub 248, as seen in FIGURES 10A and 10B. The guide member hub 248 is sized and shaped to transition between the guide member 240 and a handpiece 50 so the oscillatory movement may be applied to the guide member 240, such as during insertion of the transfer member 230. In at least one embodiment, the guide member hub 248 connects to the same handpiece 50 as used to provide oscillating motion to the penetrating member 110 or reinforcing member 120. In other embodiments, a different handpiece 50 having a different type of driving actuator 51 may be connected to the guide member hub 248 such that the oscillating motion provided to the guide member 240 is different than that previously applied to the penetrating member 110 and/or reinforcing member 120. For instance, a handpiece 50 with a piezoelectric driving actuator may be used with the penetrating member 110 and/or reinforcing member 120 to provide displacements on the order of the micron level during insertion through bone, such as cortical bone. Once the bone marrow is reached, the guide member 240 may connect to a handpiece 50 with an electromagnetic motor for a driving actuator such as provides millimeter displacements, permitting more area to be covered in the bone marrow for collection and/or delivery. In some embodiments, the same handpiece 50 may have different types of driving actuators providing different types of oscillating motion. In other embodiments, different handpieces 50 each have different types of driving actuators 51 therein. The guide member 240 may receive any type of oscillatory motion, such as but not limited to linear, longitudinal, axial, and rotational oscillating motion.

The guide member hub 248 may be made of any appropriate material(s), including metals such as stainless steel, titanium, and aluminum, plastics such as polyvinyl chloride (PVC), acrylonitrile butadiene styrene (ABS), polyethylenes and polycarbonates, polymeric compounds, and inert materials. These materials are provided for illustrative purposes and are not intended to be limiting or an exhaustive list of possible materials. The solid guide member 240 interfaces with a solid face on the guide member hub 248. The guide member hub 248 may connect to the proximal end of the guide member 240 by secure, fluid sealing connection, such as but not limited to press-fit, brazing, soldering, molding, overmolding, snap-fitting, swaging or other common plastic-plastic, metal-metal, or plastic-metal connection forming techniques.

The guide member hub 248 is further configured to interface with the handpiece 50, such as through a connection point 55. This interface mechanism may be located at the proximal end 244, and may be any configuration capable of engaging with the handpiece 50 or connection point 55 thereof, such as Luer-type fittings, tapers, threading, sliding, locking, and other structures suitable for selective engagement and disengagement. In a preferred embodiment, the guide member hub 248 is selectively releasable from the handpiece 50.

In one embodiment, there may be one or more guide members 240 fed through the transfer member lumen 234. The guide members 240 act as pull wires and may be used to manipulate the shape of the transfer member 230 after it has been inserted through the penetrating member 110. This is a similar concept to cardiac ablation catheters. Wires run through the transfer member lumen 234 from the distal end 232 to the proximal end 236 of the transfer member 230. They attach to the inside of the distal end of the transfer member 230, so when tension is applied to the wire or guide members 240 from the proximal end, the distal end 232 of the transfer member 230 deforms. By changing the shape of the transfer member 230 tip, more accurate placement and/or collection of material can be achieved, and a greater area of cells can be accessed.

As shown in FIGURE 13, the material to be delivered to the target site 3 are typically stored in a reservoir 250 such as a syringe, infusion pump, or other source that has a configuration capable of fluid sealing engagement with the transfer member hub 238. Similarly, the reservoir 250 may serve as a collection or repository for material collected from the target site 3 through the transfer member 230. In some embodiments, the reservoir 250 may also be an aspiration source, such as a syringe, to withdraw or collect material 20 from the target site, which may be stored in the reservoir 250 or a separate collection site (not shown).

In use, once the penetrating member 110 has pierced the bone and accessed the intraosseous space or other target site 3, such as the bone marrow, the transfer member 230 is fed through the penetrating member lumen 114 until the distal end 232 of the transfer member 230 extends beyond the distal tip 112 of the penetrating member 110 and is exposed in the target site. Material 20 such as stem cells, modified stem cells, hematopoietic stem cells, DNA modifying vectors, viruses, viral vectors, lentiviral vectors, lentiviral particles, DNA, DNA complexes, RNA, RNA complexes, proteins, peptides, antibodies virosomes, gene therapies,

drugs, medicines, therapeutic materials, blood, and bone marrow may be injected through the transfer member lumen 234, thereby delivering the material 20 to the bone marrow or other tissue or cells in the area of the target site 3 near the apertures 235. Flow of material 20 may occur by any method of fluid dynamics, including by diffusion or pressure differential, such as when delivery material is forced by depressing the plunger of a syringe at the proximal end of the system 200. The transfer member 230 can slide freely within the penetrating member lumen 114. Because of this, the healthcare practitioner can easily adjust the length of the transfer member 230 protruding from the penetrating member 110 to ensure the material 20 is delivered or collected at a specific site. As the length of the transfer member 230 beyond the distal tip 112 of the penetrating member 110 is increased, the amount of cells in the target site 3 that are able to be accessed are increased in tandem. In the cases where the transfer member 230 is at least partially curved, the transfer member 230 may be inserted and then rotated within the target site 3 to increase the target area radially.

In some embodiments, the transfer member 230 may be retained within the target site 3, such as the bone marrow 9, and may remain resident therein for a period of time to allow diffusion of HSCs, stem cells, viruses, or other material 20 into the target site 3 over time. In such embodiments, the penetrating member 110 may be removed from the target site 3 and bone, leaving the transfer member 230 behind. The transfer member 230 may comprise a biodegradable, bioabsorbable, bioresorbable, or degradative material such that the transfer member 230 may break down and decompose over time, and may be absorbed, resorbed, processed and/or pass through the body of the patient, further facilitating delivery of the material 20 contained or impregnated therein and eliminating the need for subsequent removal of the transfer member 230 after delivery of the material 20 to the target site 3.

As shown throughout the Figures, in some embodiments the present invention includes a system 200 for injecting material 20 such as hematopoietic stem cells and/or lentiviral particles into a patient. In at least one embodiment, as in FIGURE 13, system 200 comprises a reservoir 250 and a transfer member 230 in fluid communication with reservoir 250. As discussed further below, a penetrating member 110 is configured to penetrate skin 5 and bone 7 of the patient so that material 20 of reservoir 250 can be injected into bone marrow 9, as in

FIGURE 8. In certain embodiments, material 20 may comprise hematopoietic stem cells, and in other embodiments, material 20 may comprise lentiviral particles.

During operation of system 200, penetrating member 110 can be used to penetrate skin 5 at first skin penetration location, as shown in FIGURE 3. Penetrating member 110 can then be used to penetrate bone 5 at a first bone penetration location before being inserted into bone marrow 9. System 200 can then be used to inject material 20 (e.g. hematopoietic stem cells or lentiviral particles) into bone marrow 9, as at FIGURE 8. In certain embodiments system 200 may comprise a syringe or other suitable mechanism configured to inject material 20 into bone marrow 9.

In at least one embodiment, penetrating member 110 can be configured as a needle with sufficient stiffness and sharpness to penetrate skin 5 and bone 7. Penetrating member 110 can be used to penetrate skin 5 at a skin penetration location and bone 7 at a bone location. This process can be repeated such that penetrating member 110 penetrates bone 7 at a plurality of locations. In this manner, material 20 of reservoir 250 can be distributed or disseminated into a greater volume of bone marrow 9 than would be possible with a single penetration location.

A second exemplary embodiment, as shown in FIGURE 5, comprises a system 200 configured similar to previously-described system 200. In this embodiment, however, system 200 comprises a penetrating member 110 with a transfer member 230 configured to extend from the penetrating member 110. In certain embodiments, penetrating member 110 is configured as a needle with a sufficient stiffness and sharpness to penetrate skin 5 and bone 7, while transfer member 230 is a flexible or semi-rigid structure.

During operation, system 200 can distribute or disseminate material 20 of reservoir 250 into an extended volume of bone marrow 9 with a single skin penetration location and bone penetration location. This distribution of contents can be accomplished by inserting penetrating member 110 through skin 5 and bone 7. With penetrating member 110 inserted into bone marrow 9, transfer member 230 can be extended through and from penetrating member 110.

Material 20 (e.g. hematopoietic stem cells or lentiviral particles) can then be directed from reservoir 250, through transfer member 230, as in FIGURE 13. In certain embodiments, system 200 may comprise a syringe or other suitable mechanism configured to inject material 20 into bone marrow 9. Material 20 can then be disseminated from transfer member 230 into

bone marrow 9. In some embodiments, transfer member 230 can be withdrawn from bone marrow 9 after material 20 is injected into bone marrow 9.

In certain embodiments, transfer member 230 may be separate from penetrating member 110 so that transfer member 230 remains in bone marrow 9. In particular
5 embodiments, transfer member 230 can comprise a material that allows material 20 to diffuse from transfer member 230 into bone marrow 9 over an extended period of time (e.g. greater than one day, one week, or one month). In certain embodiments, transfer member 230 may be formed from a biodegradable material such that it can remain in bone marrow 9 until it degrades or dissolves.

10 Another embodiment comprises a system 200 that is similar to previously-described system 200. For example, system 200 comprises a reservoir 250 and a penetrating member 110 and a transfer member 230 that can extend distally from penetrating member 110. In this embodiment, as seen in FIGURES 5, 7A and 7B, transfer member 230 also comprises a plurality of apertures 235 configured to disseminate material 20 of system 200, as explained
15 in further detail below.

During operation, system 200 can also distribute or disseminate material 20 of reservoir 250 into an extended volume of bone marrow 9 with a single skin penetration location and bone penetration location. Similar to other embodiments, this distribution of material 20 can be accomplished by inserting penetrating member 110 through skin 5 (at skin penetration
20 location) and bone 7 (at bone location). With penetrating member 110 inserted into bone marrow 9, transfer member 230 can be extended through and distally from penetrating member 110.

Material 20 (e.g. hematopoietic stem cells or lentiviral particles) can then be directed from reservoir 250, through transfer member 230 (e.g. via a syringe or other suitable
25 mechanism). Material 20 can then be disseminated from transfer member 230 (e.g. via apertures 235) into bone marrow 9, as in FIGURE 8. In some embodiments, transfer member 230 can be withdrawn from bone marrow 9 after material 20 are injected into bone marrow 9.

In certain embodiments, transfer member 230 can be detached from penetrating member 110 so that transfer member 230 remains in bone marrow 9. In certain embodiments,
30 apertures 235 can be sized and distributed such that material 20 diffuse from transfer member 230 into bone marrow 9 over an extended period of time (e.g. greater than one day, one week,

or one month). In particular embodiments, apertures 235 may have a diameter of less than 1,000 microns or less than 500 microns or less than 100 microns. In certain embodiments, transfer member 230 may be formed from a biodegradable material such that it can remain in bone marrow 9 until transfer member 230 degrades or dissolves.

5 As discussed herein, exemplary embodiments of the present disclosure address shortcomings of existing IV infusion systems and methods. Exemplary embodiments place hematopoietic stem cells in the correct environment (HSC niche) to survive and proliferate. Accordingly, fewer hematopoietic stem cells will be required to repopulate the bone marrow. Exemplary embodiments can therefore reduce the requirement of hematopoietic stem cells per
10 transplant and can increase the recovery of the patient, as a higher number of the hematopoietic stem cells will contribute to repopulate the hematopoietic system.

Furthermore, exemplary embodiments may require less conditioning of the patients if partial allogeneic or transgenic chimerism is sufficient. In addition, the cost of vector production can be reduced since the hematopoietic stem cells need to be first genetically
15 modified before being infused into the patient. Accordingly, embodiments of this disclosure provide notable benefits in comparison to such systems and methods.

Since many modifications, variations and changes in detail can be made to the described preferred embodiments, it is intended that all matters in the foregoing description and shown in the accompanying drawings be interpreted as illustrative and not in a limiting sense. Thus,
20 the scope of the invention should be determined by the appended claims and their legal equivalents. Now that the invention has been described,

What is claimed is:

1. A system for penetration of bone, comprising:

a penetrating member having proximal and distal ends, a penetrating member tip at said distal end configured to pierce through bone without generation of substantial heat, a penetrating lumen extending through said penetrating member and having an opening at said penetrating member tip;

a driving actuator coupled with and configured to provide oscillating motion to said penetrating member, causing a reduction of force and heat at the interface of said penetrating member and said bone;

a transfer member selectively and adjustably positionable coaxially within said penetrating member lumen, said transfer member including flexible material along at least a portion thereof, a plurality of apertures at a distal end of said transfer member, and a transfer member lumen extending through said transfer member in fluid communication with said plurality of apertures, said transfer member configured to at least one of (i) deliver material through at least a portion of said bone to a target site, and (ii) to collect material from said target site.

2. The system as recited in claim 1, wherein said target site is at least one of intraosseous space, cancellous bone, bone marrow, marrow space, medullary cavity, and spinal cord.

3. The system as recited in claim 1, wherein said transfer member includes flexible material at said distal end.

4. The system as recited in claim 1, wherein said transfer member includes different flexible materials of different degrees of flexibility along a length of said transfer member.

5. The system as recited in claim 1, wherein said transfer member is at least one of biodegradable, bioabsorbable, bioresorbable, and decomposable.

6. The system as recited in claim 1, wherein said penetrating member tip is removably anchored in said target site, permitting direct access to said target site from beyond the bone.

7. The system as recited in claim 1, wherein said material is at least one of stem cells, modified stem cells, hematopoietic stem cells, DNA modifying vectors, viruses, viral vectors, lentiviral vectors, lentiviral particles, DNA, DNA complexes, RNA, RNA complexes, proteins, peptides, antibodies, virosomes, gene therapies, drugs, medicines, therapeutic materials, blood, and bone marrow.

8. The system as recited in claim 1, wherein at least one of said penetrating member and said transfer member includes a protective layer configured to affect at least one of thermal conductivity, friction, preservation of said material, detect the presence of a predefined material, and detect temperature.
- 5 9. The system as recited in claim 1, wherein said transfer member is steerable at said target site.
10. The system as recited in claim 1, further comprising a reinforcing member selectively positionable within said penetrating member lumen and providing at least one of increased rigidity and heat dissipation to said penetrating member.
- 10 11. The system as recited in claim 10, wherein said reinforcing member is connectable to said driving actuator and receives oscillatory motion.
12. The system as recited in claim 10 wherein said reinforcing member is selectively attachable to a handpiece through a reinforcing member hub, wherein said handpiece includes said driving actuator.
- 15 13. The system as recited in claim 10, wherein said penetrating member includes a penetrating member hub having a side port in fluid communication with said penetrating member lumen and configured to provide thermal control fluid to said penetrating member lumen and exterior of said reinforcing member to reduce heat of at least one of said penetrating member and said target site.
14. The system as recited in claim 1, further comprising a guide member selectively
20 positionable within said transfer member lumen for insertion to said target site, and selectively removable from said transfer member lumen prior to delivery or collection of said material.
15. The system as recited in claim 14, wherein said guide member is connectable to said driving actuator and receives oscillatory motion.
16. The system as recited in claim 15, further comprising plurality of driving actuators
25 configured to provide different types of oscillatory motion, wherein said penetrating member is connectable to a first one of said plurality of driving actuators and receives a first type of oscillatory motion, and said guide member is connectable to a second one of said plurality of driving actuators and receives a second type of oscillatory motion, and wherein said plurality of driving actuators may be included in the same handpiece or different handpieces.

17. The system as recited in claim 1, further comprising a handpiece including said drive actuator, wherein said penetrating member releasably attaches to said handpiece through a penetrating member hub.

18. The system as recited in claim 1, further comprising a reservoir of said material in fluid communication with at least one of said penetrating member and said transfer member lumen and capable of providing or collecting said material to or from said target site therethrough.

19. The system as recited in claim 1, further comprising an aspiration source in fluid communication with at least one of said penetrating member and said transfer member lumen and capable of providing negative pressure to pull said material from said target site.

20. A method of penetrating bone, comprising:

activating a drive actuator to generate oscillating motion in an attached penetrating member;

advancing said penetrating member through bone without generation of substantial heat;

advancing said penetrating member into a target site through at least a portion of said bone;

stopping advancement of said penetrating member when said target site is reached;

advancing a transfer member having a plurality of apertures through said penetrating member to said target site; and

performing at least one of (i) delivering material to said target site through said transfer member and said plurality of apertures, and (ii) collecting material from said target site into said transfer member through said plurality of apertures.

21. The method as recited in claim 20, further comprising aligning said penetrating member at an angle of insertion relative to an entry surface, wherein said angle of insertion is an oblique angle.

22. The method as recited in claim 21, wherein said angle of insertion is in the range of 10° to 90°.

23. The method as recited in claim 20, further comprising selectively positioning a reinforcing member coaxially within said penetrating member for insertion and removing said reinforcing member from said penetrating member prior to advancing said transfer member through said penetrating member.

24. The method as recited in claim 20, further comprising selectively positioning a guide member coaxially within said transfer member for advancement through said penetrating member

and removing said guide member from said transfer member prior to delivering or collecting material.

25. The method as recited in claim 20, further comprising rotating said penetrating member during at least one of insertion and advancement to said target site.

5 26. The method as recited in claim 18, further comprising steering said transfer member at said target site.

27. The method as recited in claim 20, wherein delivering material to said target site occurs over an extended period of time that is at least one of (i) greater than one day, (ii) greater than one week, and (iii) greater than one month.

10 28. The method as recited in claim 20, wherein delivering or collecting material includes delivering or collecting at least one of stem cells, modified stem cells, hematopoietic stem cells, DNA modifying vectors, viruses, viral vectors, lentiviral vectors, lentiviral particles, DNA, DNA complexes, RNA, RNA complexes, proteins, peptides, antibodies, virosomes, gene therapies, drugs, medicines, therapeutic materials, blood, and bone marrow.

15 29. The method as recited in claim 28, wherein said method includes injecting lentiviral particles to said target site prior to injecting hematopoietic stem cells to said target site.

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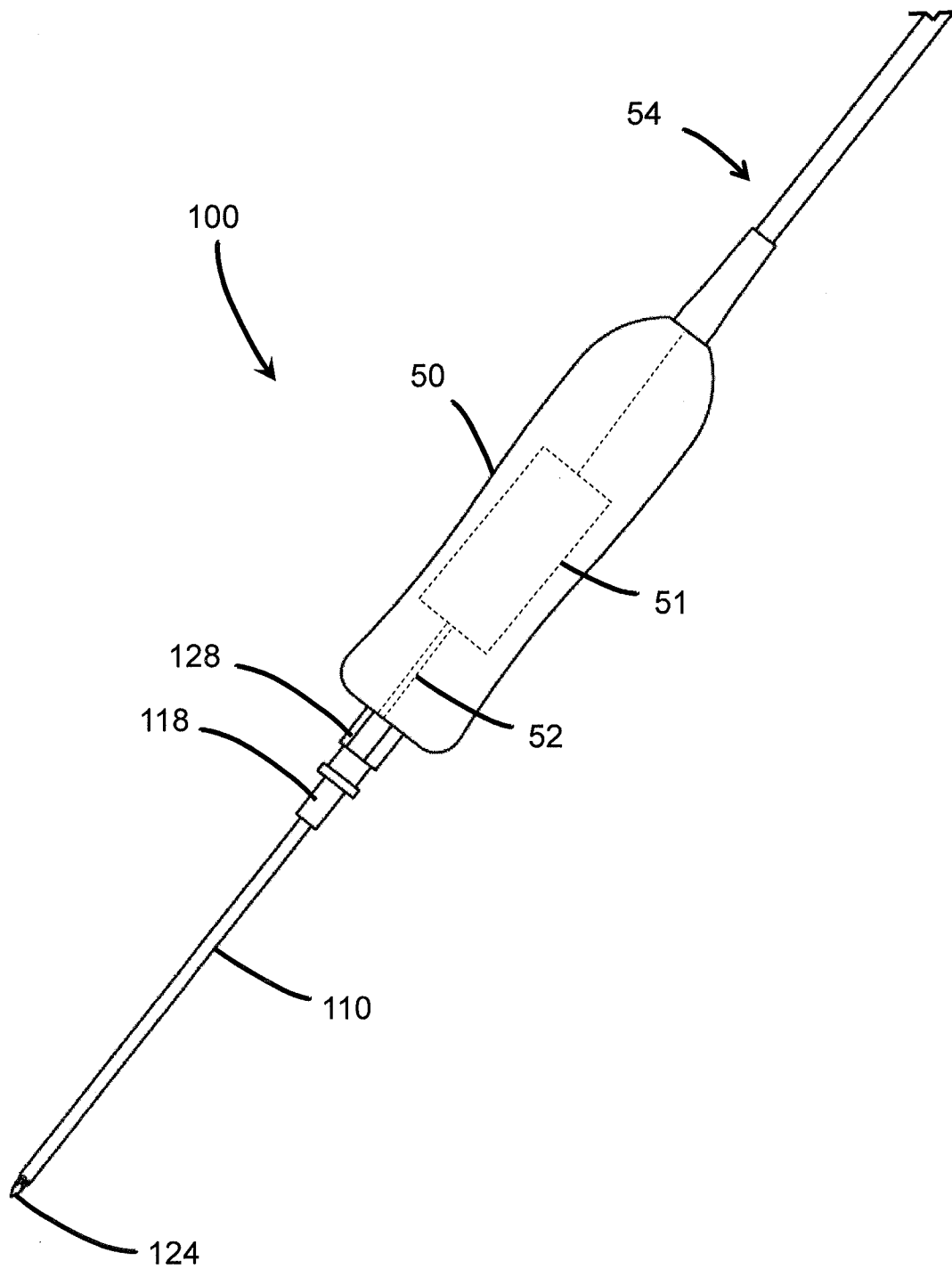
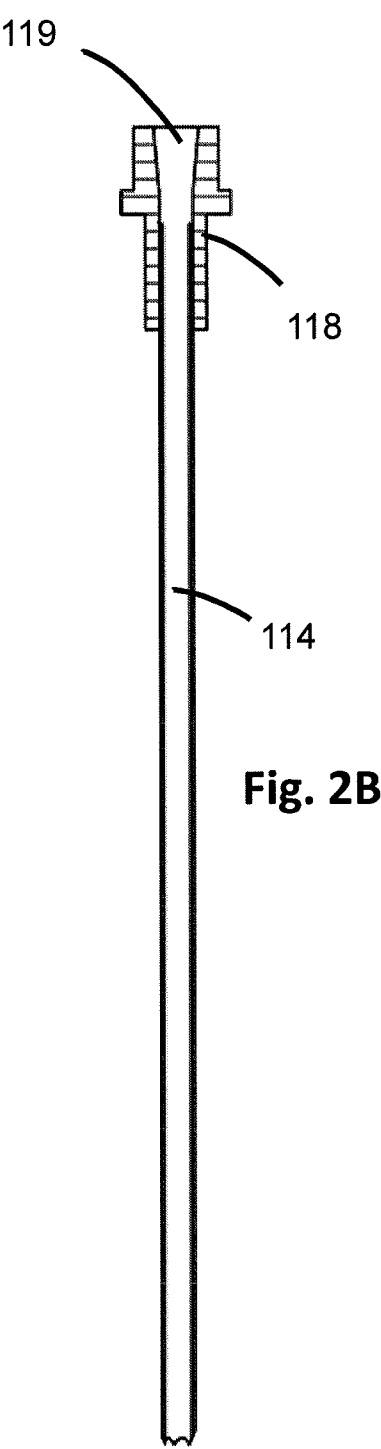
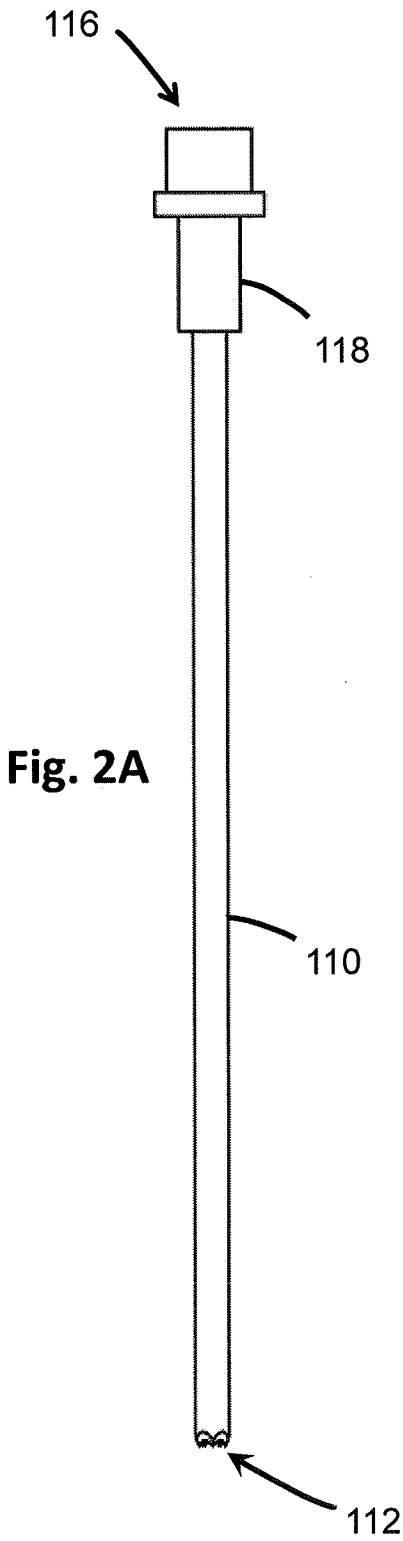
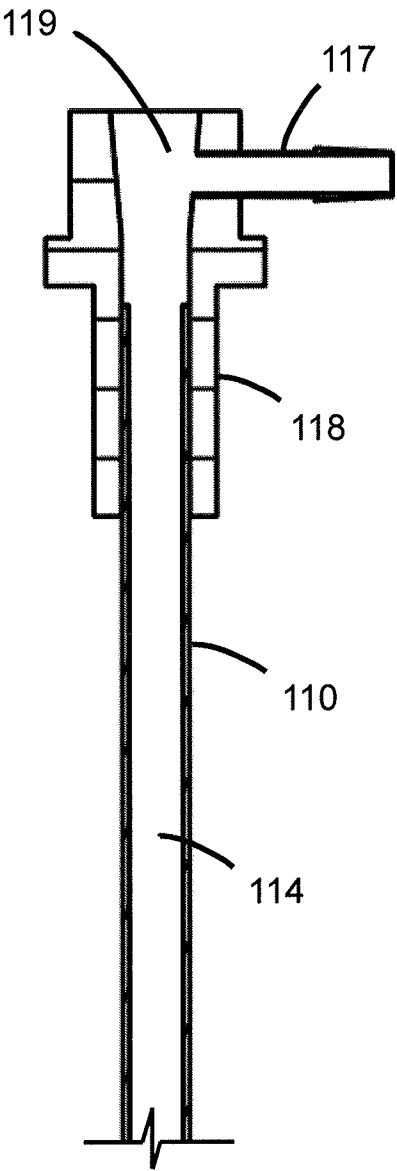
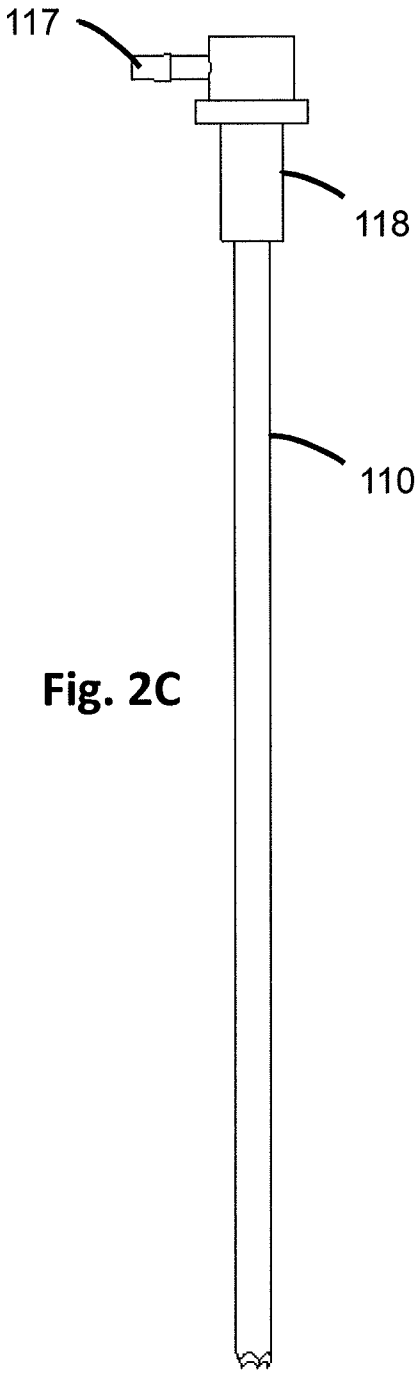


Fig. 1





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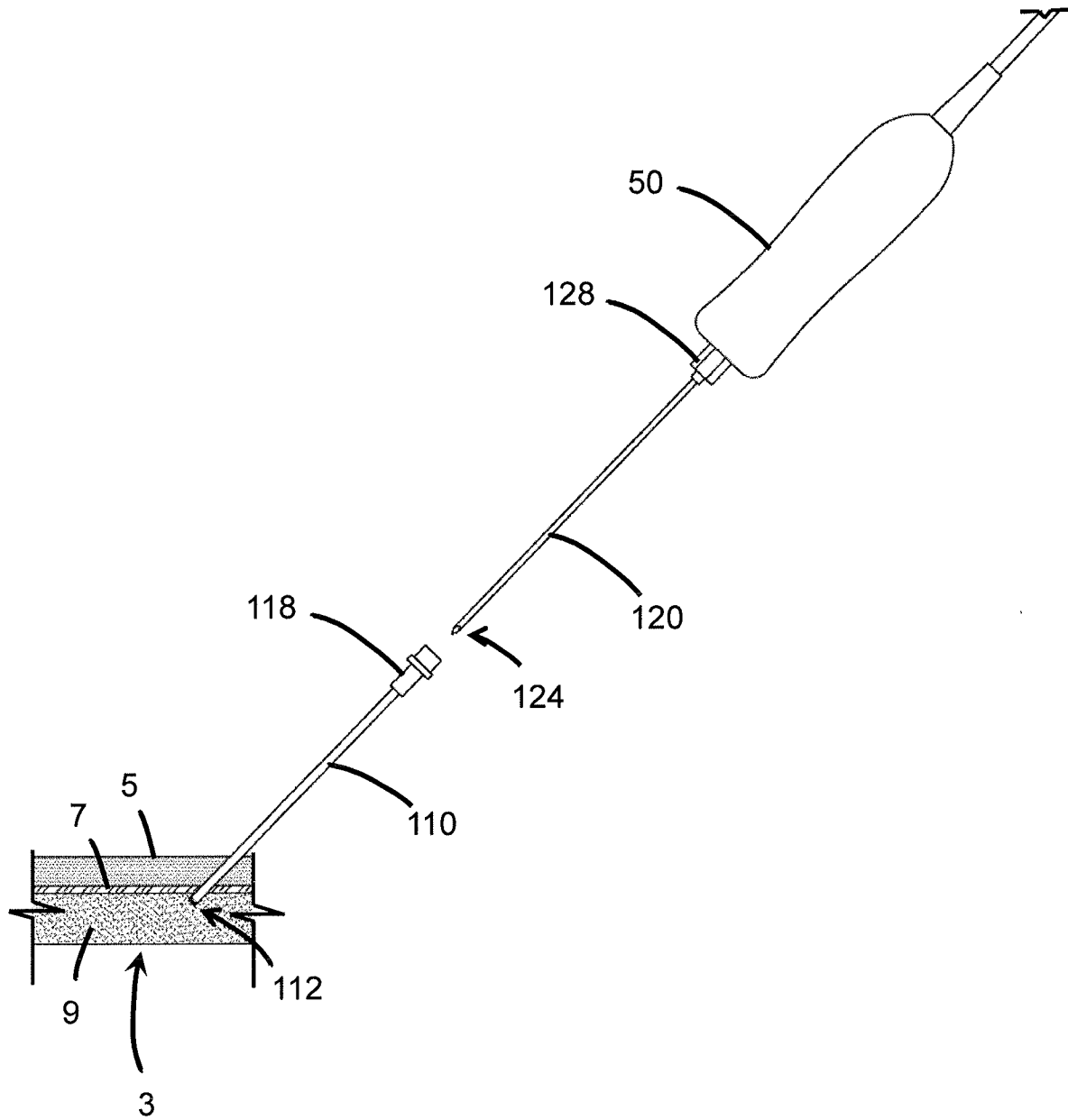


Fig. 3

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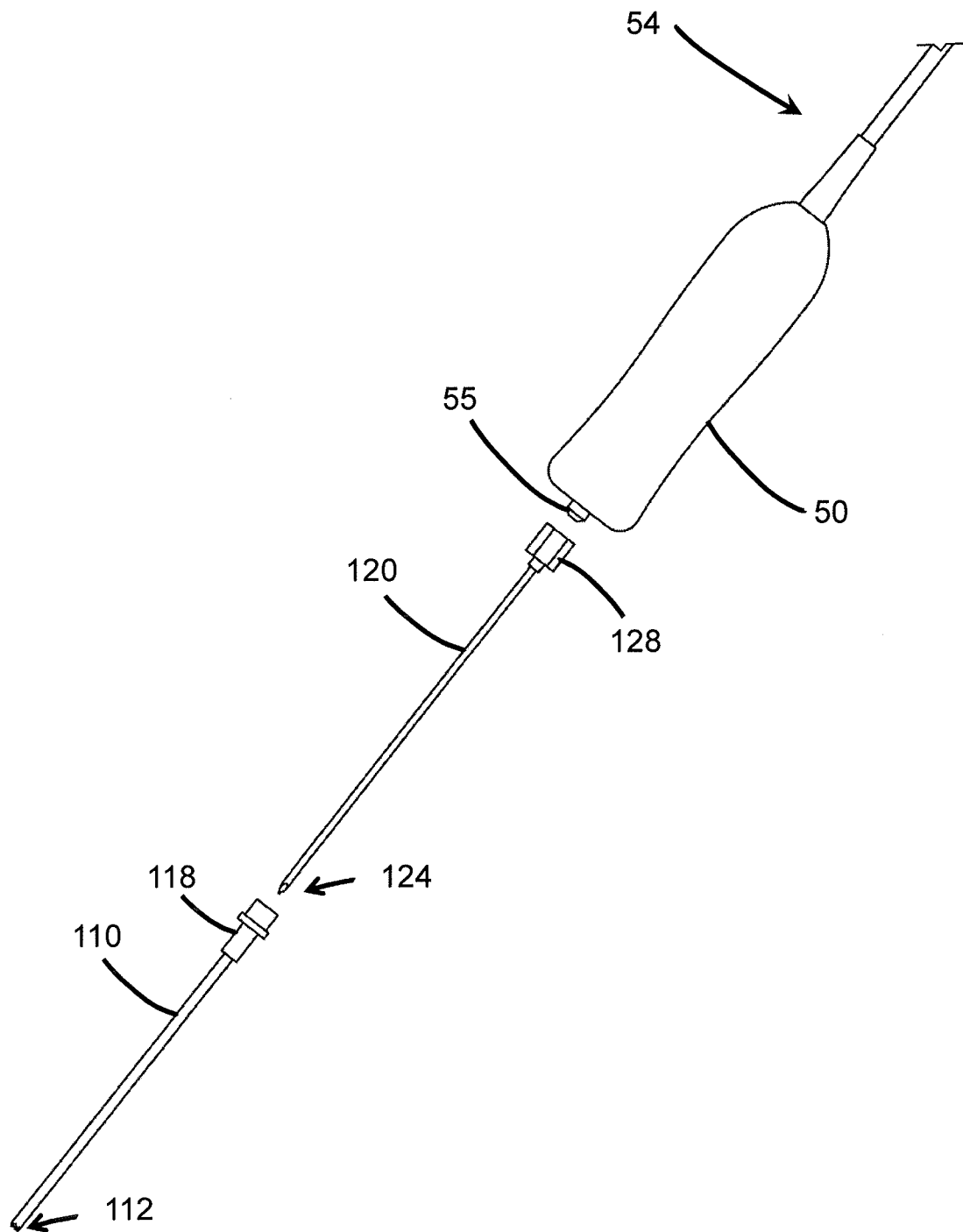


Fig. 4

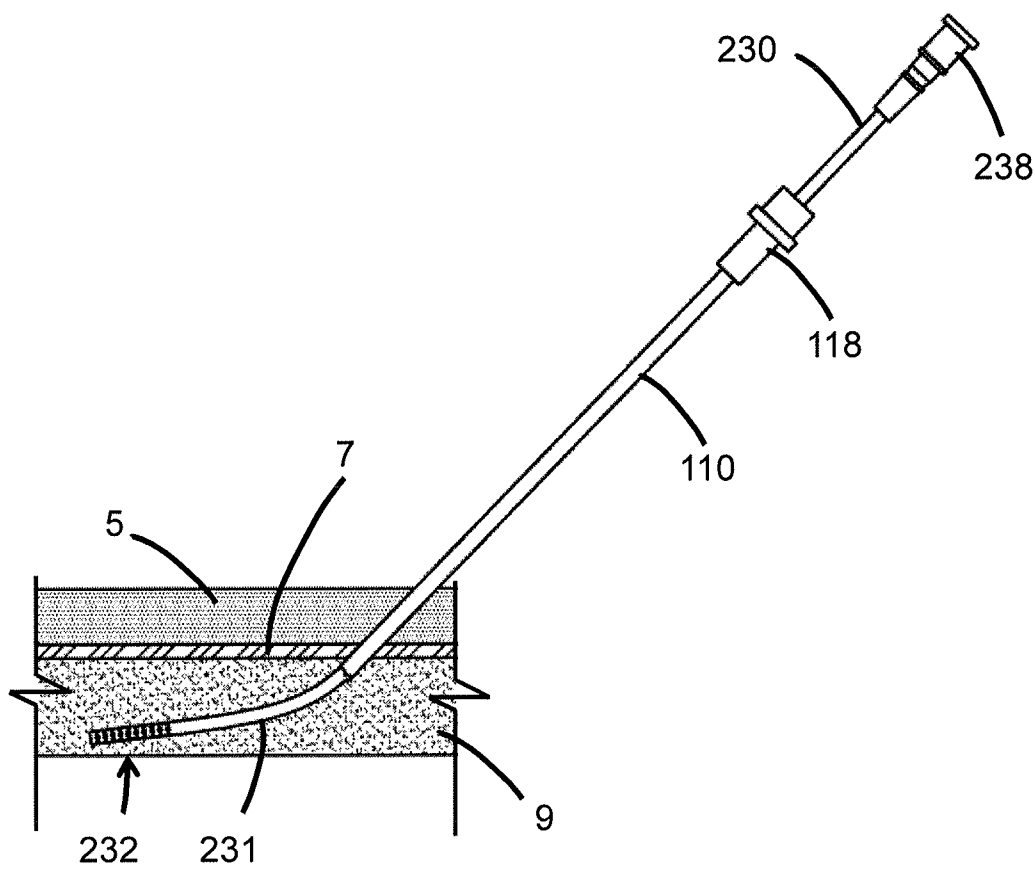


Fig. 5

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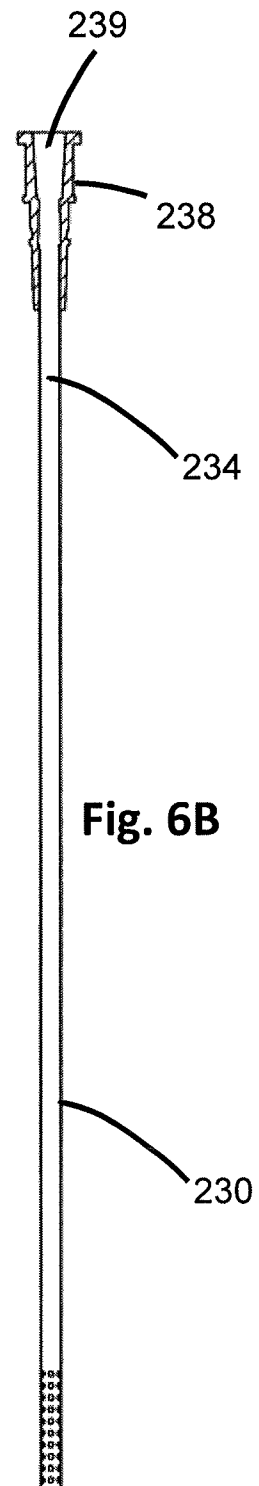
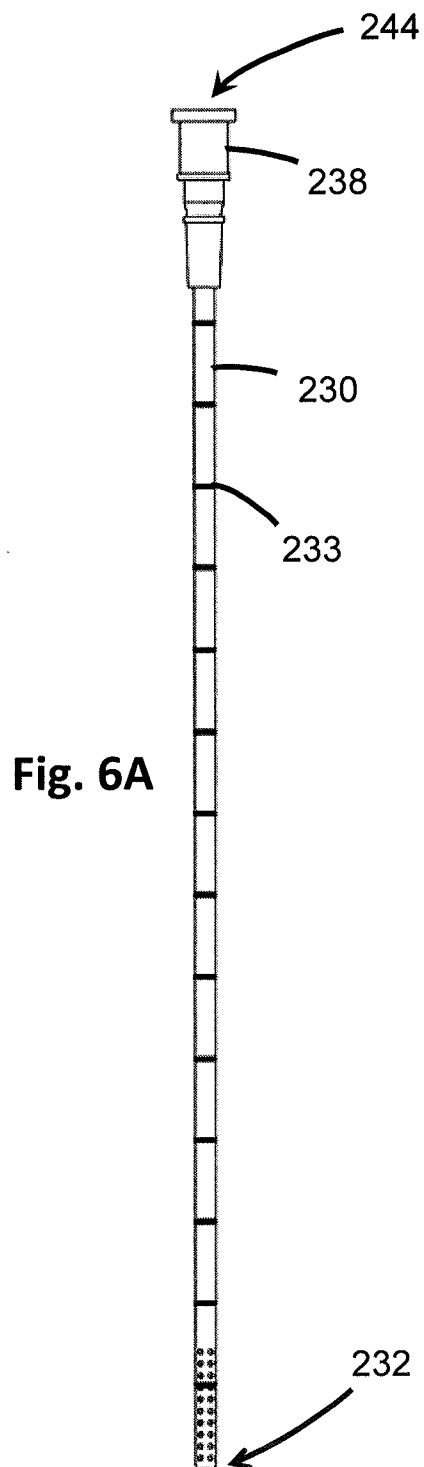


Fig. 7A

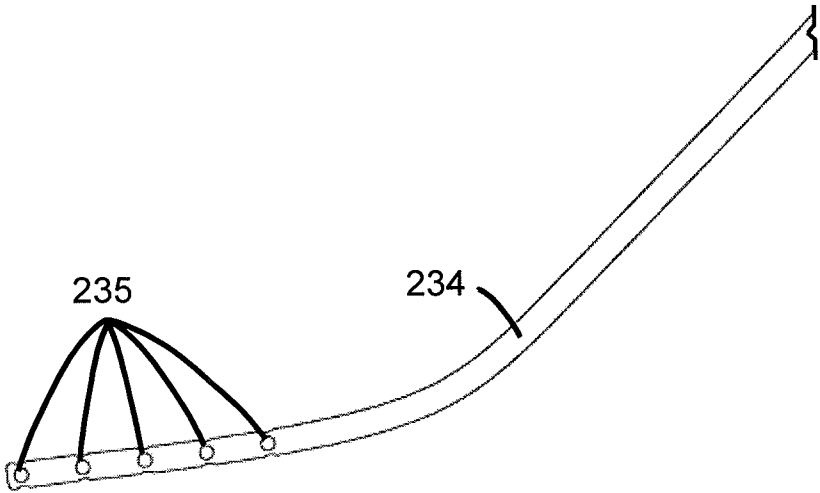
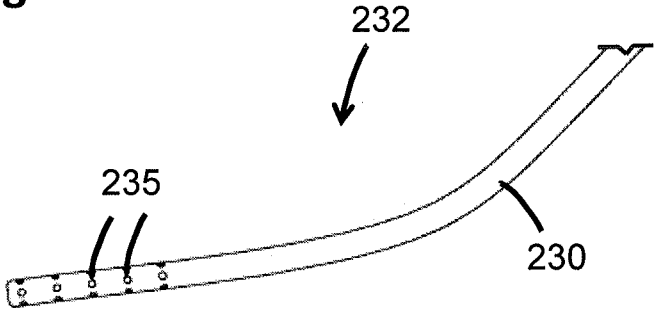


Fig. 7B

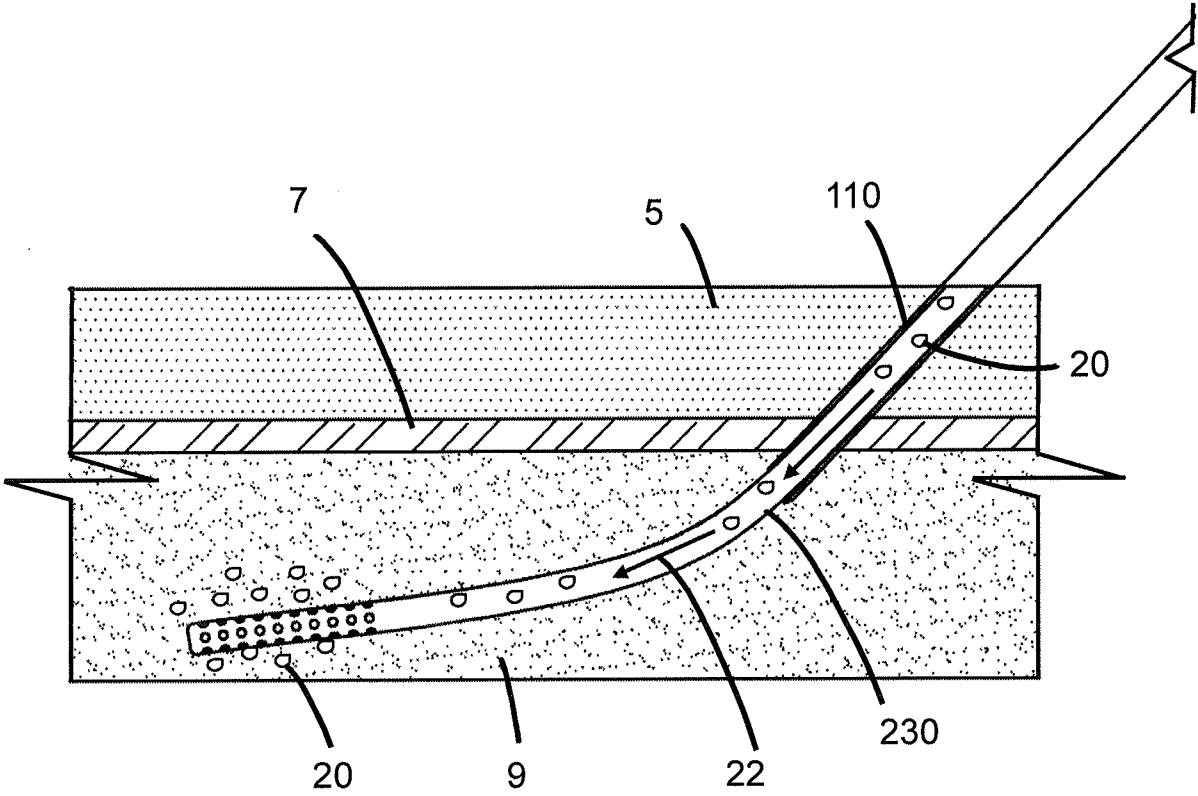


Fig. 8

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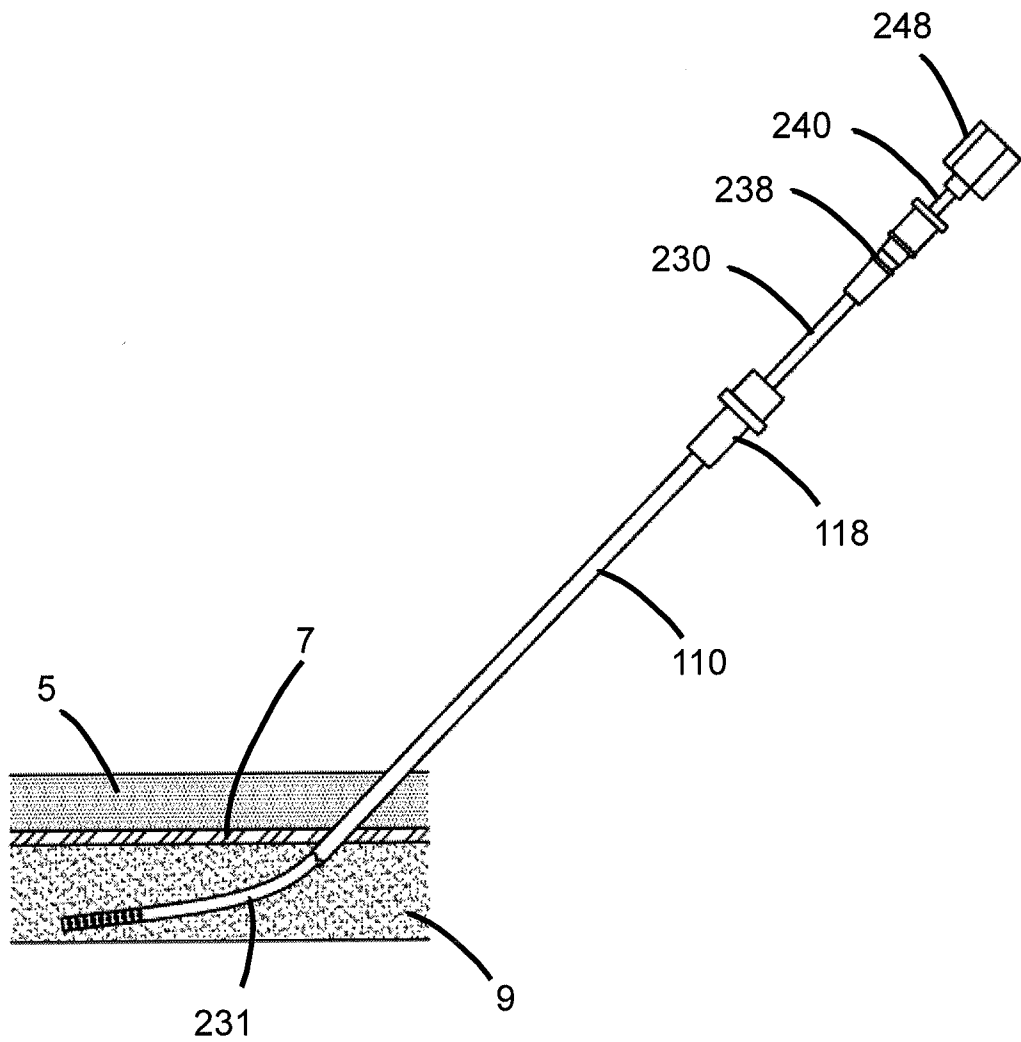
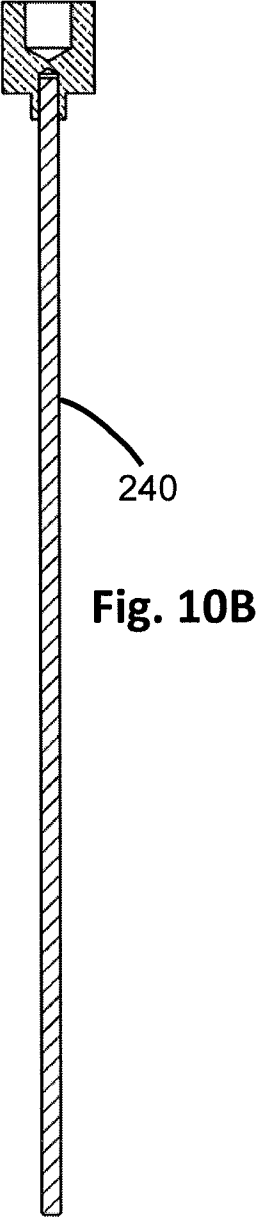
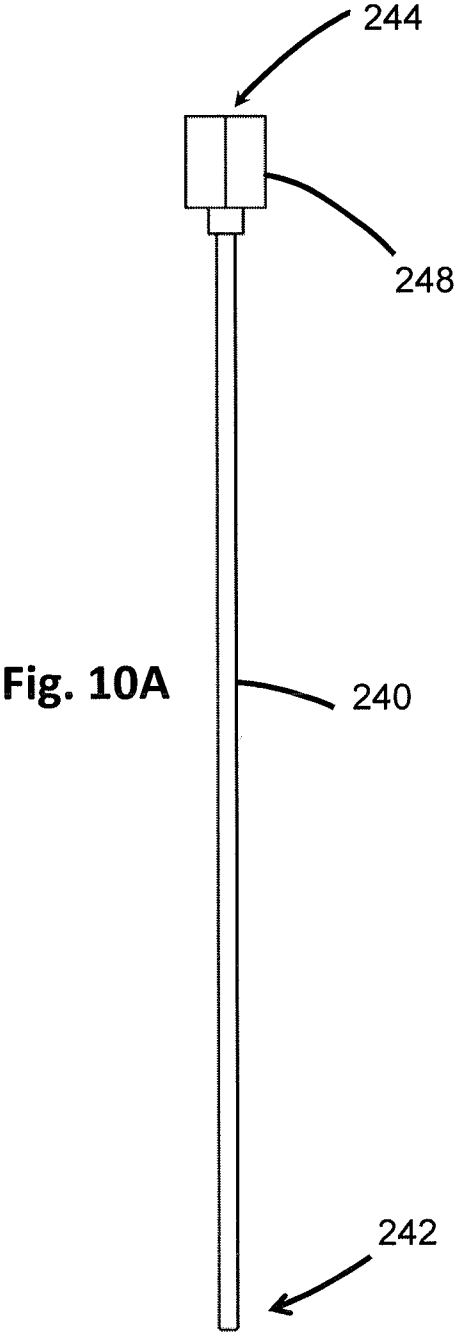
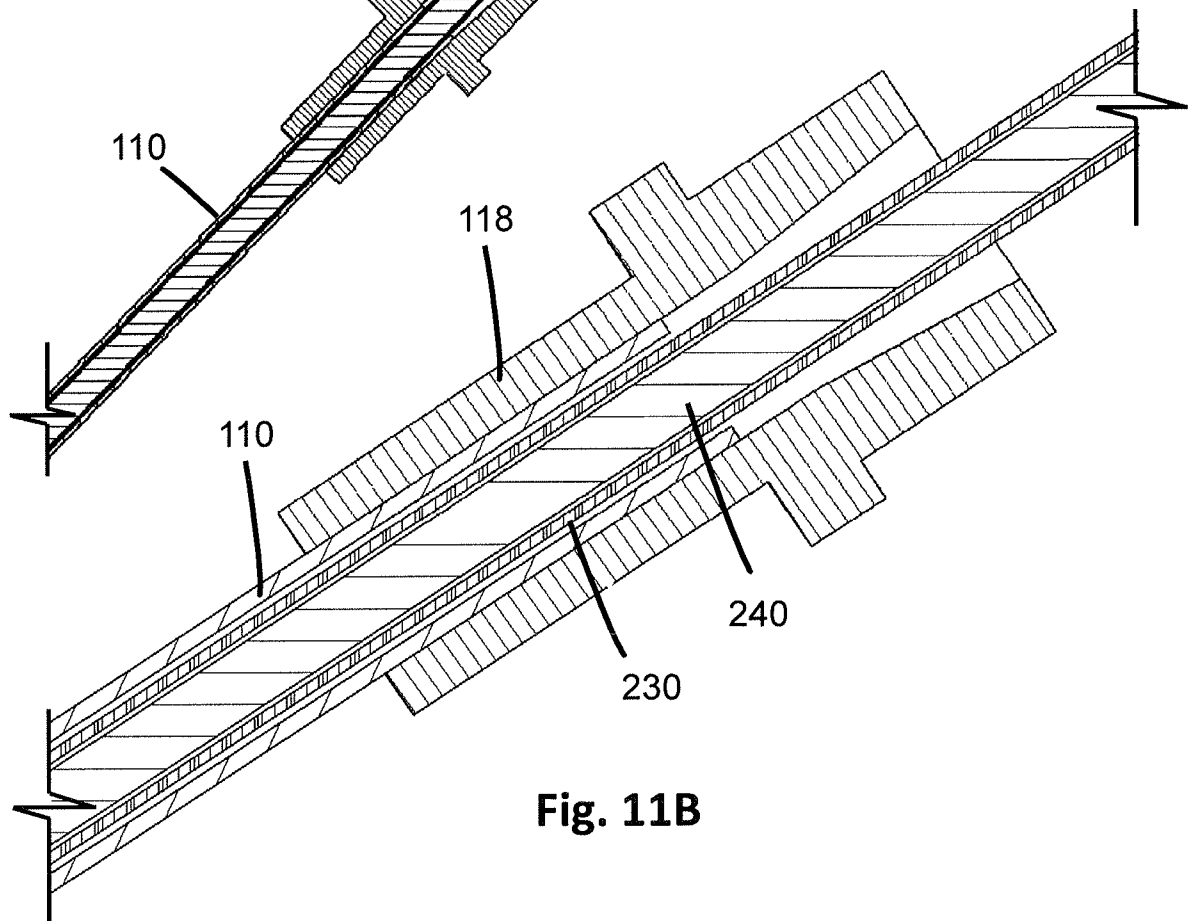
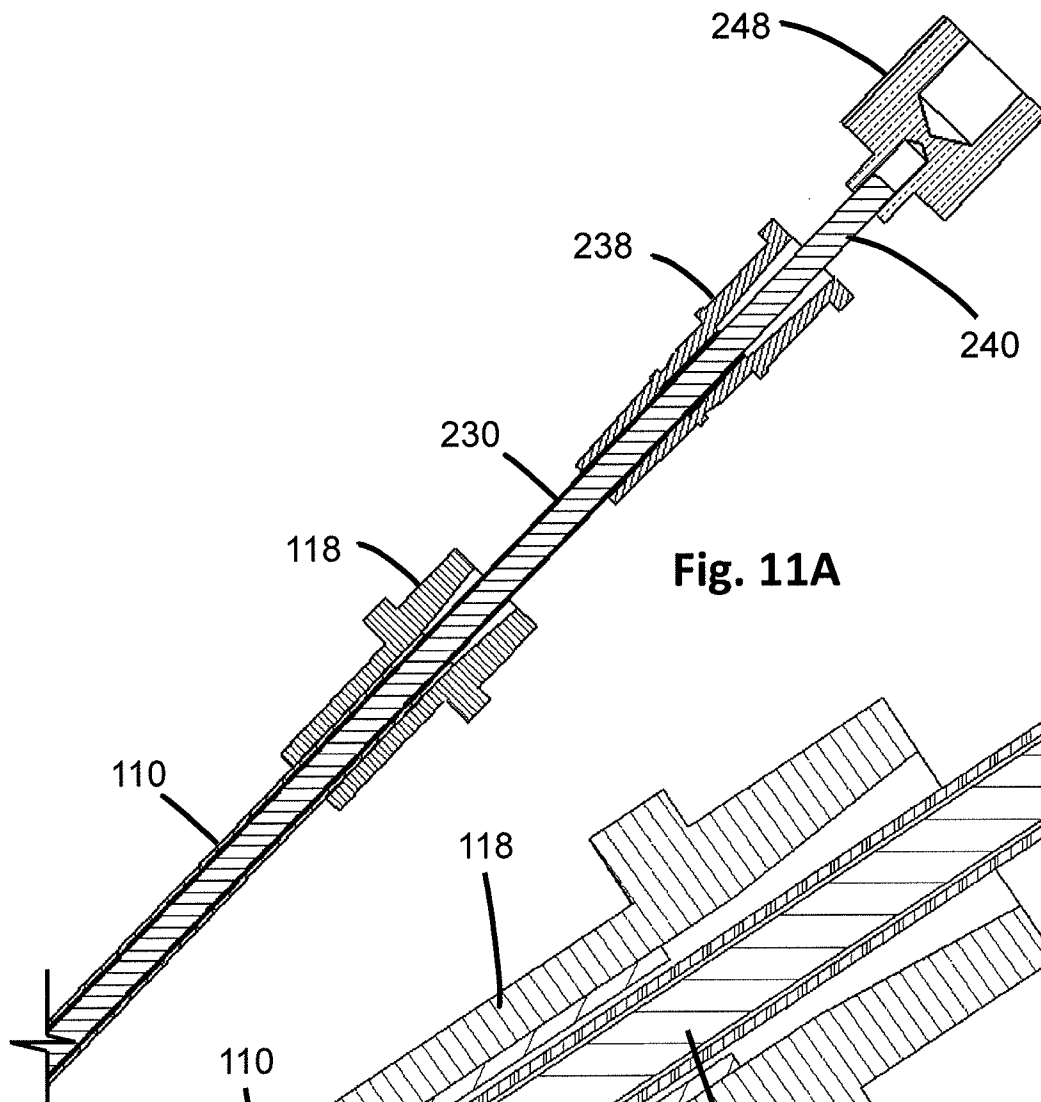


Fig. 9

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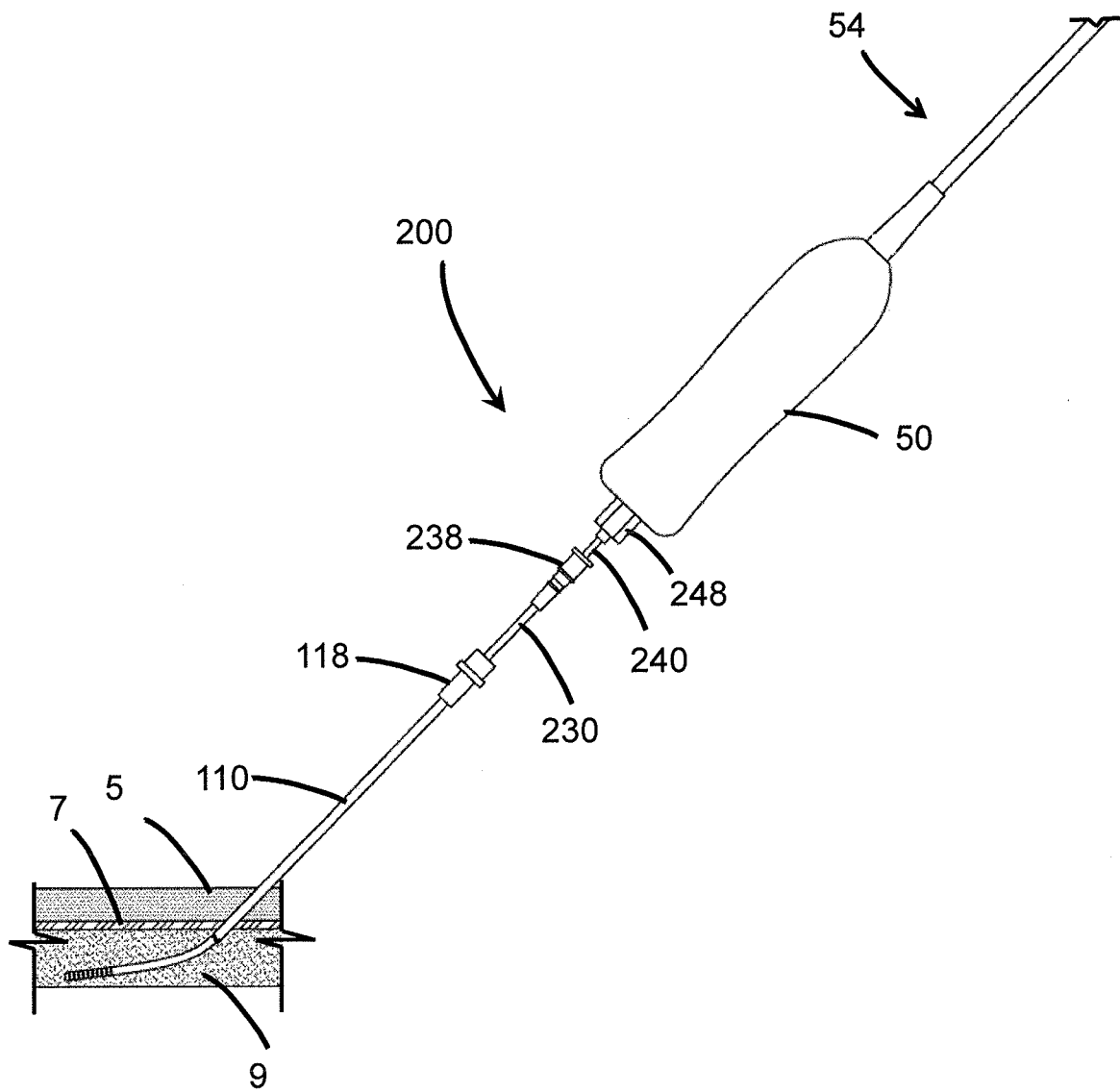


Fig. 12

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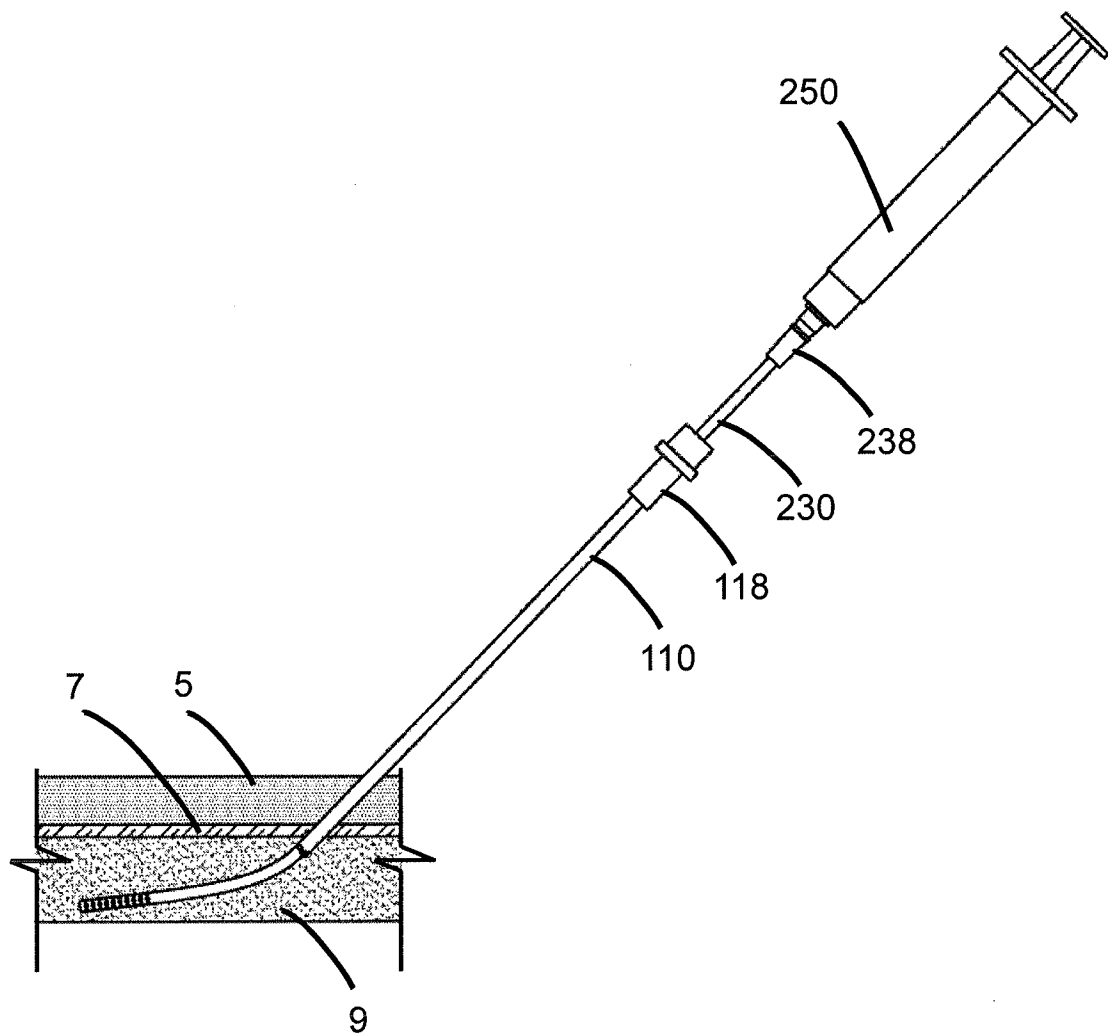


Fig. 13

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 17/40436

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61B 10/02, A61B 17/34, A61B 17/32 (2017.01)

CPC - A61B 10/025, A61B 17/3472, A61B 2010/0258, A61B 2017/320084, A61B 2017/32007, A61B 17/320068, A61M 2202/10

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.
A	US 2007/0276352 A1 (Crocker et al.), 29 November 2007 (29.11.2007), entire document, especially Abstract, Fig. 1, 4 and 7; para [0074]-[0078], [0091]-[0094] and [0121]	1-29
A	US 2015/0182232 A1 (Peterson et al.), 02 July 2015 (02.07.2015), entire document, especially Fig. 1; para [0035], [0040], [0048] and [0073]	1-29
A	US 7,462,181 B2 (Kraft et al.), 09 December 2008 (09.12.2008), entire document	1-29
A	US 8,328,738 B2 (Frankhouser et al.), 11 December 2012 (11.12.2012), entire document	1-29
A	US 8,777,871 B2 (Frankhouser et al.), 15 July 2014 (15.07.2014), entire document	1-29
A	WO 2015/084881 A1 (TRINITY ORTHOPEDICS, LLC), 11 June 2015 (11.06.2015), entire document	1-29
A	US 2003/0225344 A1 (Miller), 04 December 2003 (04.12.2003), entire document	1-29

☐ 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

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Date of the actual completion of the international search

05 September 2017

Date of mailing of the international search report

25 SEP 2017

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