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(54) Title: MULTI-COMPONENT INJECTION SYSTEM AND METHODS FOR TISSUE REPAIR

(57) Abstract: The present disclosure provides devices, kits and methods for preparing injections with cells and carrier components for delivery to a target area in the body. The disclosed devices, kits, and methods provide preparation and monitoring of injections.

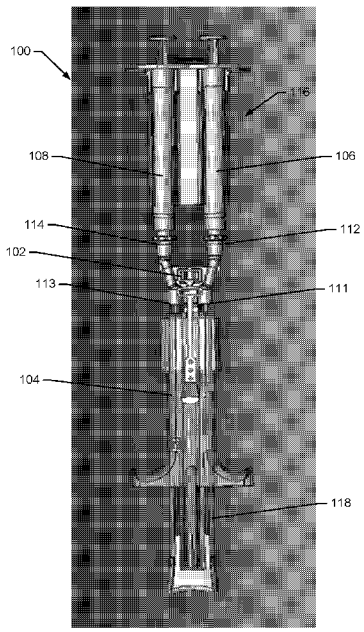

FIG. 1

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MULTI-COMPONENT INJECTION SYSTEM AND METHODS FOR TISSUE REPAIR

Field of the Invention

[0001] The present disclosure relates generally to medical injection devices, methods and kits, and in particular to medical injection devices for preparing an injection of a multi-component composition for repair of a tissue defect.

Background of the Invention

[0002] Recent advances in cell-based medical therapies include the development of an injectable, cell-based fluid composition that can be injected into damaged or diseased tissue to repair the tissue. For example, an injectable cell-based fluid composition can be used for resolving back pain associated with degenerative disease of the intervertebral disc. The treatment involves the combination of two components in a single fluid stream for injection directly into the disc, via a spinal injection needle placed in the target intervertebral disc. However, the injection components may need to remain separate until reaching the target, so that the components polymerize within the target and not while injecting the components. Therefore, there is a need for preparing an injection but keeping the injection components separate.

[0003] Furthermore, the cells may be within a cryovial that is not sterile on the outside, but the cells on the inside must remain sterile. Devices and methods for preparing and delivering cells from a cryovial to a fully sterile delivery area and mixing the cells with the injection components, while maintaining the separation of the components are therefore needed.

[0004] Additionally, the injection pressure at the needle-tip can, if excessive, cause further damage to already compromised tissue. To avoid further damage to already compromised tissue, injection pressure must somehow be monitored and controlled. Various approaches to doing so are theoretically possible, but pressure cut-offs are not clear, and certain monitoring/control

approaches can further complicate treatment by reducing the accuracy of fluid delivery to the tissue. Devices and methods for monitoring and controlling injection pressure for injection of a therapeutic fluid composition are therefore needed.

Summary of the Invention

[0005] In one aspect, the present disclosure provides an injection preparation device including a body to reversibly engage a multi-barrel carrier syringe, a cell delivery syringe and a carrier delivery syringe. The body may include a first transfer portion defining a first inlet to reversibly couple to a first barrel of the multi-barrel carrier syringe, and a second inlet to reversibly couple to the barrel of the cell delivery syringe and a second transfer portion defining a third inlet configured to reversibly couple to a second barrel of the multi-barrel carrier syringe, a fourth inlet to reversibly couple to the barrel of the carrier delivery syringe. The first inlet and second inlet communicate through a first conduit through the body and the third and fourth inlets communicate through a second conduit through the body. The body, such as the first inlet, may reversibly couple to a cell transfer syringe. At least one of the first, second, third, and fourth inlets include a female connector port projecting from the body, where each female connector port may receive the injection end of a barrel of the carrier syringe or the delivery syringe. At least one of the first, second, third, and fourth inlets include a male connector port projecting from the body, where each male connector port may reversibly engage a female connector coupled to a barrel of the carrier syringe or the delivery syringe. At least one of the first, second, third, and fourth inlets may include a luer connector.

[0006] In another aspect, the present disclosure provides an injection preparation kit including the injection preparation described herein above, and at least one of a multi-barrel carrier syringe, a cell transfer syringe, a cell delivery syringe and a carrier delivery syringe. At least one or more of the multi-barrel carrier syringe, cell transfer syringe, cell delivery syringe and carrier delivery syringe may be coupled to the body. The multi-barrel carrier syringe, cell delivery syringe and carrier delivery syringe may be coupled to the body. The carrier

syringe may include two barrels and a double-barrel plunger rod assembly to transfer a first predetermined amount of a first carrier component and a second predetermined amount of a second carrier component. The kit may include the cell delivery syringe and the carrier delivery syringe or the cell transfer syringe. In one aspect, the cell transfer syringe may be a single-barrel syringe.

[0007] In another aspect, the present disclosure provides an injection preparation device including a body adapted to reversibly couple to a multi-barrel carrier syringe and a multi-barrel delivery syringe, the body having a first transfer portion defining a first inlet configured to reversibly couple to a first barrel of the multi-barrel carrier syringe and a second inlet configured to reversibly couple to a first barrel of the multi-barrel delivery syringe and a second transfer portion defining a third inlet configured to reversibly couple to a second barrel of the multi-barrel carrier syringe, and a fourth inlet configured to reversibly couple to a second barrel of the multi-barrel delivery syringe. The first inlet and second inlet communicate through a first conduit through the body and the third and fourth inlets communicate through a second conduit through the body. The body may reversibly couple to a cell transfer syringe, for example, the first inlet may reversibly couple to the cell transfer syringe. At least one of the first, second, third and fourth inlets includes a female connector port projecting from the body, where each female connector port may receive the injection end of a barrel of one of the carrier or delivery syringes. At least one of the first, second, third, and fourth inlets includes a male connector port projecting from the body, each male connector port may reversibly engage a female connector coupled to a barrel of the carrier syringe or the delivery syringe. At least one of the first, second, third and fourth inlets may include a luer connector.

[0008] In another aspect, the present disclosure provides an injection preparation kit including the injection preparation device described herein above, and at least one of the multi-barrel carrier syringe, the multi-barrel delivery syringe and the cell transfer syringe. At least one or more of the multi-barrel carrier syringe, the multi-barrel delivery syringe and the cell transfer syringe may be coupled to the body. In one aspect, the multi-barrel carrier syringe and the

multi-barrel delivery syringe may be coupled to the body. In another aspect, the multi-barrel delivery syringe and the cell transfer syringe may be coupled to the body. The multi-barrel delivery syringe may include two barrels and a double-barrel plunger rod assembly. The kit may include the multi-barrel delivery syringe or the cell transfer syringe. The cell transfer syringe may be a single-barrel syringe.

[0009] In another aspect, the present disclosure provides an injection preparation device including a body to reversibly engage a multi-barrel carrier syringe, a cell transfer syringe, a cell delivery syringe and a carrier delivery syringe, the body including a first transfer portion defining a first inlet to reversibly couple to a first barrel of the multi-barrel carrier syringe, a second inlet to reversibly couple to the barrel of the cell delivery syringe, and a fifth inlet to reversibly couple to the barrel of the cell transfer syringe, and a second transfer portion defining a third inlet to reversibly couple to a second barrel of the multi-barrel carrier syringe, a fourth inlet to reversibly couple to the barrel of the carrier delivery syringe. The first, second, and fifth inlets communicate through a first conduit through the body and the third and fourth inlets communicate through a second conduit through the body. At least one of the first, second, third, fourth and fifth inlets may include a female connector port projecting from the body, where each female connector port may receive the injection end of a barrel of the carrier syringe or the delivery syringe. At least one of the first, second, third, fourth and fifth inlets may include a male connector port projecting from the body, where each male connector port may reversibly engage a female connector coupled to a barrel of the carrier syringe or the delivery syringe. At least one of the first, second, third, fourth and fifth inlets may include a luer connector. The first transfer portion may include a two-way valve to limit a fluid path between the first and second inlets or between the first and fifth inlets. The third inlet defined by the second transfer portion may include a one-way valve.

[0010] In another aspect, the present disclosure provides an injection preparation kit includes the injection preparation device described herein above, and at least one of a multi-barrel carrier syringe, a cell transfer syringe, a cell

delivery syringe and a carrier delivery syringe. At least one or more of the multi-barrel carrier syringe, cell transfer syringe, cell delivery syringe and carrier delivery syringe may be coupled to the body. The multi-barrel carrier syringe, cell delivery syringe and carrier delivery syringe may be coupled to the body. The injection preparation kit may include the multi-barrel carrier syringe. The injection preparation kit may include the multi-barrel delivery syringe, where delivery syringe includes two barrels and a double-barrel plunger rod assembly. The injection preparation kit may include the cell transfer syringe. The cell transfer syringe may be a single-barrel syringe.

[0011] In another aspect, the present disclosure provides an injection preparation device including a body adapted to reversibly couple to a multi-barrel carrier syringe, a multi-barrel delivery syringe and a cell transfer syringe, the body having a first transfer portion defining a first inlet to reversibly couple to a first barrel of the multi-barrel carrier syringe, a second inlet to reversibly couple to a first barrel of the multi-barrel delivery syringe, and a fifth inlet to reversibly couple to the cell transfer syringe, and a second transfer portion defining a third inlet configured to reversibly couple to a second barrel of the multi-barrel carrier syringe, and a fourth inlet configured to reversibly couple to a second barrel of the multi-barrel delivery syringe. The first inlet, second inlet and fifth inlet communicate through a first conduit through the body and the third and fourth inlets communicate through a second conduit through the body. At least one of the first, second, third, fourth and fifth inlets may include a female connector port projecting from the body, where each female connector port may receive the injection end of a barrel of one of the carrier, delivery or cell transfer syringes. At least one of the first, second, third, fourth and fifth inlets may include a male connector port projecting from the body, each male connector port may reversibly engage a female connector coupled to a barrel of the carrier syringe or the delivery syringe. At least one of the first, second, third, fourth and fifth inlets may be a luer connector. The first transfer portion may include a two-way valve to limit a fluid path between the first and second inlets or between the first and fifth inlets. The second inlet defined by the second transfer portion may include a one-way valve.

[0012] In another aspect, the present disclosure provides an injection preparation kit including the injection preparation device described herein above and at least one of the multi-barrel carrier syringe, the multi-barrel delivery syringe and the cell transfer syringe. At least one or more of the multi-barrel carrier syringe, the multi-barrel delivery syringe and the cell transfer syringe may be coupled to the body. The multi-barrel carrier syringe and the multi-barrel delivery syringe may be coupled to the body. The injection preparation kit includes the multi-barrel delivery syringe, where the delivery syringe includes two barrels and a double-barrel plunger rod assembly. The injection preparation kit includes the cell transfer syringe. The cell transfer syringe may be a single-barrel syringe.

[0013] In another aspect, the present disclosure provides a transfer shield for use with a cell storage container having an opening covered by a sterile seal capable of penetration by a hollow needle. The transfer shield may include a body having a first surface and a second surface and define an opening therethrough from the first surface to the second surface, the opening having a rim; a substantially tubular projection from the first surface defining a wall surrounding the opening; and the hollow needle disposed perpendicular to the first surface from within the wall. The hollow needle may be coupled to the rim of the opening and the hollow needle may have a length less than or equal to a depth of the tubular projection from the first surface. The body may be substantially planar. The transfer shield may include a connector port projecting from the body second surface, where the connector port defines a wall surrounding the opening and where the connector port may engage a syringe barrel. The connector port may include a female luer port to reversibly engage a male luer-tipped syringe. The wall of the substantially tubular projection may define an opening therethrough so that the contents of the cell storage container may be visible when the shield is in use to penetrate the seal by contacting the seal with the hollow needle. The transfer shield may include a removable adhesive sterile barrier disposed over the opening through the body.

[0014] In another aspect, the present disclosure provides an injection preparation kit for transferring a prepared cell composition from a cell storage

container to a cell transfer syringe. The kit may include at least one of the injection preparation devices described herein above and the transfer shield. The injection preparation may include a cell storage container including a substantially cylindrical body defining a central lumen, a first end and a second end, wherein the first end defines a vent port and a fill port, and the second end defines an access port, and a flexible sealing element over the access port, wherein the vent port, fill port and access port communicate with the central lumen. The injection preparation kit may include a cell storage container including a substantially cylindrical body defining a central lumen, a first end and a second end, where the first end defines a fill opening, and the second end defines an access port and a flexible sealing element over the access port; and a cap configured to seal the fill opening, where the fill opening and access port communicate with the central lumen. The flexible sealing element may include a rubber septum. The cell storage container has an inner surface and an outer surface, where the inner surface may be sterile and the outer surface may be non-sterile. The cell storage container contains a prepared cell composition for transfer to a delivery syringe. The second end may further define a connector port for reversibly engaging a connector port of a second device. The cell storage container may operate with an automated filling machine.

[0015] The injection preparation kit may further include an amount of the prepared cell composition. The injection preparation kit may further include an amount of at least a first carrier component. The injection preparation kit may further include an amount of a second carrier component, where the amounts of the first and the second carrier components are packaged separately. The first and the second carrier components when combined form a polymerized hydrogel.

[0016] In another aspect, the present disclosure provides a combination of at least one of any one of the injection preparation devices and transfer shield described herein above in combination with an injection load monitoring device to reversibly couple to a delivery syringe. The injection load monitoring device may include a mechanical load sensor having an amplifier and an electrical coupling coupled thereto for coupling to a pressure display unit; a syringe adapter coupled

to the mechanical load sensor, the syringe adapter having a first surface configured to engage an outward end portion of a plunger rod of a plunger rod assembly of the delivery syringe; and a finger plate coupled to the mechanical load sensor. The mechanical load sensor may be selected from a miniature or subminiature load cell and a piezoresistive mechanical load sensor. The mechanical load sensor may be operable for measuring a compression load of up to about 100 lb. The mechanical load display unit displays a visual alarm, an auditory alarm, or both in response to the mechanical load applied to the delivery syringe. The mechanical load display unit may be directly coupled to the syringe adapter or finger plate. The pressure display unit is configured for wireless communication with the mechanical load sensor.

[0017] The injection preparation kit may further include a Y-connector to reversibly couple to a multi-barrel delivery syringe. The Y-connector includes a connector body having a first end and a second end, the first end defining at least two connector inlets for reversibly coupling the Y-connector to the at least two barrels of the delivery syringe; a dual lumen cannula coupled to the second end of the connector body; and a spinal needle coupled to the dual lumen cannula. In an aspect, the injection preparation kit may further include a light source or light conduit. The light source may be used to expose a photoactivated polymer(s) at or near the end of the cannula. In various aspects, the light source and/or light conduit may be associated with the Y-connector, spinal needle, or delivery syringe.

[0018] In another aspect, the present disclosure provides any combination described herein further including an amount of at least a first carrier component. The combination further including an amount of a second carrier component, where the amounts of the first and the second carrier components are packaged separately. The first and the second carrier components when combined form a polymerized hydrogel.

[0019] In another aspect, the present disclosure provides a method of preparing a multi-component injection, including obtaining a carrier syringe including at least two barrels with a first carrier component in a first barrel and a

second carrier component in a second barrel; coupling a first barrel of the carrier syringe to the first inlet of an injection preparation device, and a second barrel of the carrier syringe to the third inlet of the injection preparation device; coupling a cell delivery syringe to the second inlet of the injection preparation device; coupling a carrier delivery syringe to the fourth inlet of the injection preparation device; and transferring the first carrier component from the first barrel of the carrier syringe to the cell delivery syringe through the first conduit of the injection preparation device; and transferring the second carrier component from the second barrel of the carrier syringe to the carrier delivery syringe through the second conduit of the injection preparation device, where dual plunger rod assembly used with the carrier syringe may be configured to transfer a predetermined amount of the first carrier component to the cell delivery syringe and a predetermined amount of the second carrier component to the carrier delivery syringe. The method may further include coupling a cell transfer syringe to the injection preparation device. The cell transfer syringe may be coupled to the first inlet of the injection preparation device. The method may further include: removing the carrier syringe from the injection preparation device; coupling a cell transfer syringe to the injection preparation device, where the cell transfer syringe contains a cell composition; transferring the first carrier component from the cell delivery syringe to the cell transfer syringe though the first conduit, whereby the first carrier component is mixed with the cell composition to form a first cell/carrier mixture; and transferring the first cell/carrier mixture back to the cell delivery syringe through the first conduit.

[0020] In another aspect, the present disclosure provides a method of preparing a multi-component injection, including: filling a carrier syringe including at least two barrels with a first carrier component in a first barrel and a second carrier component in a second barrel; coupling the two barrels of the carrier syringe to the first and third inlets of an injection preparation device, coupling the two barrels of the delivery syringe to the second and fourth inlets of the injection preparation device, and transferring the first carrier component from the first barrel of the carrier syringe to a first barrel of the delivery syringe through the first conduit of the injection preparation device, and the second carrier component from the

second barrel of the carrier syringe to a second barrel of the delivery syringe through the second conduit of the injection preparation device, where a plunger used with the carrier syringe may be configured to transfer a predetermined amount of the first carrier component and a predetermined amount of the second carrier component to the delivery syringe. The method further including: removing the carrier syringe from the injection preparation device; coupling a cell transfer syringe to the injection preparation device, where the cell transfer syringe contains a cell composition; transferring the first carrier component from the first barrel of the delivery syringe to the cell transfer syringe though the first conduit, whereby the first carrier component is mixed with the cell composition to form a first cell/carrier mixture; and transferring the first cell/carrier mixture back to the first barrel of the delivery syringe through the first conduit. The cell transfer syringe may be coupled to the first inlet of the of the injection preparation device. The method may further include decoupling the delivery syringe from the injection preparation device, where the first barrel of the delivery syringe contains the first cell/carrier mixture and the second barrel of the delivery syringe contains the second carrier component.

[0021] In another aspect, the present disclosure provides a method of preparing a multi-component injection, including: obtaining a carrier syringe includes at least two barrels with a first carrier component in a first barrel and a second carrier component in a second barrel; coupling a first barrel of the carrier syringe to the first inlet of the injection preparation device, and a second barrel of the carrier syringe to the third inlet of the injection preparation device; coupling a cell delivery syringe to the second inlet of the injection preparation device; coupling a cell transfer syringe to the fifth inlet of the injection preparation device; coupling a carrier delivery syringe to the fourth inlet of the injection preparation device; and transferring the second carrier component from the second barrel of the carrier syringe to the carrier delivery syringe through the second conduit of the injection preparation device; limiting the flow path through the first conduit of the injection preparation device to between the first inlet and the fifth inlet, and transferring the first carrier component from the first barrel of the carrier syringe to the cell transfer

syringe through the first conduit of the injection preparation device, where a dual plunger rod assembly used with the carrier syringe is configured to transfer a predetermined amount of the first carrier component to the cell transfer syringe and a predetermined amount of the second carrier component to the delivery syringe, whereby the first carrier component mixes with the contents of the cell transfer syringe; and limiting the flow path through the first conduit of the injection preparation device to between the fifth inlet and the second inlet, and transferring the mixture in the cell transfer syringe to the cell delivery syringe. The method further including decoupling the cell delivery syringe and the carrier delivery syringe from the injection preparation device, where the carrier delivery syringe contains the first second carrier component and the cell delivery syringe contains a first cell/carrier mixture.

[0022] In another aspect, the present disclosure provides a method of preparing a multi-component injection, including: filling a carrier syringe including at least two barrels with a first carrier component in a first barrel and a second carrier component in a second barrel; coupling the two barrels of the carrier syringe to the first and third inlets of an injection preparation device, coupling the two barrels of the delivery syringe to the second and fourth inlets of the injection preparation device, and transferring the first carrier component from the first barrel of the carrier syringe to a first barrel of the delivery syringe through the first conduit of the injection preparation device, and the second carrier component from the second barrel of the carrier syringe to a second barrel of the delivery syringe through the second conduit of the injection preparation device, where a plunger used with the carrier syringe is configured to transfer a predetermined amount of the first carrier component and a predetermined amount of the second carrier component to the delivery syringe. The method further including: removing the carrier syringe from the injection preparation device; coupling a cell transfer syringe to the injection preparation device, where the cell transfer syringe contains a cell composition; transferring the first carrier component from the first barrel of the delivery syringe to the cell transfer syringe though the first conduit, whereby the first carrier component is mixed with the cell composition to form a first cell/carrier

mixture; and transferring the first cell/carrier mixture back to the first barrel of the delivery syringe through the first conduit. The method further including decoupling the delivery syringe from the injection preparation device, where the first barrel of the delivery syringe contains the first cell/carrier mixture and the second barrel of the delivery syringe contains the second carrier component.

[0023] In any of the methods described herein, the method may further include coupling the delivery syringe to a Y-connector having a stem portion, and ejecting the first cell/carrier mixture from the first barrel of the delivery syringe or the cell delivery syringe and the second carrier component from the second barrel of the delivery syringe or the carrier delivery syringe through the Y-connector, whereby the first cell/carrier mixture and the second carrier component are combined in the Y-connector stem portion to form a cell/carrier composition. The methods further including injecting the cell/carrier composition into a tissue defect. The tissue may include bone, cartilage or soft tissue. The methods may further include injecting the cell/carrier composition into a degenerated intervertebral disc. The Y-connector may be configured to reversibly couple to the cell delivery syringe and to the carrier delivery syringe, and the Y-connector includes a connector body having a first end and a second end, the first end defining at least two connector inlets for reversibly coupling the Y-connector to the cell delivery syringe and the carrier delivery syringe or to the at least two barrels of the delivery syringe; the method further including coupling a dual lumen cannula to the second end of the Y-connector body, and coupling a spinal needle to the dual lumen cannula.

[0024] In any of the methods described herein, the method may further include providing a light source or light conduit for exposing a photoactivated polymer(s) at or near the end of the cannula. In various aspects, the light source and/or light conduit may be associated with the Y-connector, spinal needle, or delivery syringe.

[0025] In any of the methods described herein, the method may further include monitoring the injection load using an injection load monitoring device reversibly coupled to the cell delivery syringe, the injection load monitoring device including a mechanical load sensor having an amplifier and an electrical coupling

coupled thereto for coupling to a pressure display unit; a syringe adapter coupled to the mechanical load sensor, the syringe adapter having a first surface configured to engage an outward end portion of a plunger rod of a plunger rod assembly of the delivery syringe; and a finger plate coupled to the mechanical load sensor. The method may further include monitoring the injection load using an injection load monitoring device reversibly coupled to the delivery syringe, the injection load monitoring device including: a mechanical load sensor having an amplifier and an electrical coupling coupled thereto for coupling to a pressure display unit; a syringe adapter coupled to the mechanical load sensor, the syringe adapter having a first surface configured to engage an outward end portion of a plunger rod of a plunger rod assembly of the delivery syringe; and a finger plate coupled to the mechanical load sensor. The mechanical load sensor is selected from a miniature or subminiature load cell and a piezoresistive force sensor. The mechanical load sensor may be operable for measuring a compression load of up to about 100 lb. The pressure display unit displays a visual alarm, an auditory alarm, or both in response to the pressure applied to the delivery syringe. The pressure display unit may be directly coupled to the syringe adapter or finger plate. The pressure display unit is coupled to the mechanical load sensor wirelessly. The delivery syringe contains a prepared cell composition.

[0026] In any of the devices, kits and methods described herein, any combination described herein may include the cell storage container and further include a prepared cell composition. The prepared cell composition may include cells selected from adipocytes, neuronal stem cells, chondrocytes, notochordal cells, chondrogenic cells, mesenchymal stem cells, hematopoietic stem cells, and any pluripotent stem cells, including embryonic and induced pluripotent stem cells. The prepared cell composition may include mesenchymal stem cells derived from at least one of bone marrow, adipose tissue, synovium, periosteum, post-partum connective tissue, placenta, cord blood, and umbilical cord.

[0027] In any of the devices, kits and methods described herein, the carrier syringe may include two barrels and a double-barrel plunger rod assembly configured to transfer a first predetermined amount of a first carrier component and

a second predetermined amount of a second carrier component. The double-barrel plunger rod assembly may include a first plunger rod for slidably engaging the first barrel of the carrier syringe and a second plunger rod for slidably engaging the second barrel of the carrier syringe, where the first plunger rod is shorter than the second plunger rod so that the first predetermined amount of the first carrier component is less than the second predetermined amount of the second carrier component.

[0028] In any of the devices, kits and methods described herein, the first carrier component may be thrombin and the second carrier component may be fibrinogen. The first and/or the second carrier component may include polymers selected from: poly(ethylene glycol) (PEG), poly(ethylene oxide) (PEO), poly(vinyl alcohol) (PVA), PEG–polystyrene copolymers (PEG)–(PST), polylactic acid (PLA), ethylene glycol–lactic acid copolymers, ethylene glycol–lactic acid–caprolactone copolymers, poly(d,l-lactide-*co*-ε-caprolactone), (poly)-anhydrides, anhydrides, urethanes, polysaccharides, dextran, collagen, hyaluronic acid, diethyl fumarate/poly(propylene fumarate), chitosan, a caprolactone polymer such as polycaprolactone (PCL), polyglycolic acid (PGA), or a copolymer of polylactic acid and polyglycolic acid (PLGA), and combinations thereof. In another aspect, the first carrier component may be a photoactive polymerizing polymer and the first carrier component may further include a photoinitiator. The first predetermined amount may be about 0.5 to about 0.7 cc and the second predetermined amount may be about 1.0 to about 1.2 cc. In one aspect, the first predetermined amount may be about 0.6 cc and the second predetermined amount may be about 1.1 cc.

Brief Description of the Figures

[0029] **Fig. 1** is a drawing of a four-inlet injection preparation device with a multi-barrel carrier syringe and a multi-barrel delivery syringe.

[0030] **Fig. 2A** is a perspective view of a five-inlet injection preparation device with a multi-barrel carrier syringe and a multi-barrel delivery syringe. **Fig.**

2B is a top view of a five-inlet injection preparation device with a multi-barrel carrier syringe and a multi-barrel delivery syringe.

[0031] **Fig. 3** is a drawing of a five-inlet injection preparation device with a cell delivery syringe and a multi-barrel delivery syringe.

[0032] **Fig. 4A** is a photograph of two aspects of the cell storage container. **Fig. 4B** is a photograph of one aspect of the cell storage container in an open disposition. **Fig. 4C** is a photograph of one aspect of the cell storage container in a closed disposition.

[0033] **Fig. 5A** is perspective view of one aspect of the transfer shield with a cell storage container. **Fig. 5B** is a front view of one aspect of the transfer shield with a cell storage container. **Fig. 5C** is a drawing of a cell storage container and a tubular projection of the transfer shield in one aspect. **Fig. 5D** is a drawing of a cell storage container seal punctured by a needle in the tubular projection of the transfer shield in one aspect.

[0034] **Fig. 6** is a drawing of a second transfer shield with a cell storage container in one aspect.

[0035] **Fig. 7** is a drawing of a Y-connector for coupling to the delivery syringe and dual lumen cannula.

[0036] **Fig. 8** is a drawing of an injection load monitoring device on a multi-barrel delivery syringe in an aspect.

[0037] **Figs. 9A-E** are drawings of the injection load monitoring device with a multi-barrel delivery syringe in various aspects.

[0038] **Fig. 10** is a schematic of a method of preparing an injection using a four-inlet injection preparation device.

[0039] **Fig. 11** is a schematic of a method of preparing an injection using a five-inlet injection preparation device.

Detailed Description of the Disclosure

[0040] Unless otherwise defined herein, scientific and technical terms used in connection with the present disclosure shall have the meanings that are commonly understood by those of ordinary skill in the art. The meaning and scope

of the terms should be clear, however, in the event of any latent ambiguity, definitions provided herein take precedent over any dictionary or extrinsic definition. Further, unless otherwise required by context, singular terms as used herein and in the claims shall include pluralities and plural terms shall include the singular.

[0041] The use of "or" means "and/or" unless stated otherwise. Furthermore, the use of the term "including", as well as other forms, such as "includes" and "included", is not limiting. Also, terms such as "element" or "component" encompass both elements and components comprising one unit and elements and components that comprise more than one subunit unless specifically stated otherwise.

[0042] The present disclosure encompasses devices, systems, kits and methods for conveniently and efficiently preparing and then delivering by injection a tissue repair composition comprising multiple components that must be combined prior to the injection. Any such tissue repair composition which is obtained by the combination of multiple components is contemplated. Such tissue repair compositions include but are not limited to cell-based compositions comprising a cell composition combined with at least a carrier, for example a protein or protein-based carrier, and the carrier itself may be comprised of multiple components.

A. Injection Preparation Devices

i. 4-inlet Injection Preparation Device

[0043] Fig. **1** is a drawing of an injection preparation device with four inlets **100**. In one aspect, the four-inlet injection preparation device **100** includes a body **102** to reversibly engage a multi-barrel carrier syringe **104**, a cell delivery syringe **106** and a carrier delivery syringe **108**. The body **102** may include a first transfer portion defining a first inlet **111** to reversibly couple to a first barrel of the multi-barrel carrier syringe **104**, and a second inlet **112** to reversibly couple to the barrel of the cell delivery syringe **106** and a second transfer portion defining a third inlet **113** configured to reversibly couple to a second barrel of the multi-barrel

carrier syringe **104**, a fourth inlet **114** to reversibly couple to the barrel of the carrier delivery syringe **108**. The first inlet and second inlet communicate through a first conduit through the body **102** and the third and fourth inlets communicate through a second conduit through the body **102**. The body **102**, for example, the first inlet **111**, may reversibly couple to a cell transfer syringe (not shown).

[0044] At least one of the first, second, third, and fourth inlets **111-114** may include a female connector port projecting from the body, where each female connector port may receive the injection end of a barrel of the carrier syringe **104** or a delivery syringe **106**, **108**. At least one of the first, second, third, and fourth inlets **111-114** may include a male connector port projecting from the body, where each male connector port may reversibly engage a female connector coupled to a barrel of the carrier syringe **104** or a delivery syringe **106**, **108**. In one aspect, at least one of the first, second, third, and fourth inlets **111-114** may include a luer connector.

[0045] In another aspect, the present disclosure provides a four-inlet injection preparation device **100**, where the cell delivery syringe **106** and the carrier delivery syringe **108** may be multiple barrels of a multi-barrel delivery syringe **116**. This aspect may include a body **102** adapted to reversibly couple to a multi-barrel carrier syringe **104** and a multi-barrel delivery syringe **116**, the body **102** having a first transfer portion defining a first inlet **111** configured to reversibly couple to a first barrel of the multi-barrel carrier syringe **104** and a second inlet **112** configured to reversibly couple to a first barrel of the multi-barrel delivery syringe **116** and a second transfer portion defining a third inlet **113** configured to reversibly couple to a second barrel of the multi-barrel carrier syringe **104**, and a fourth inlet **114** configured to reversibly couple to a second barrel of the multi-barrel delivery syringe **116**. The first inlet and second inlet **111,112** communicate through a first conduit through the body and the third and fourth inlets **113,114** communicate through a second conduit through the body. The body **102** may reversibly couple to a cell transfer syringe (not shown). For example, the first inlet **111** may reversibly couple to the cell transfer syringe.

[0046] At least one of the first, second, third and fourth inlets **111-114** may include a female connector port projecting from the body **102**, where each female connector port may receive the injection end of a barrel of one of the carrier or delivery syringes **104, 116**. At least one of the first, second, third, and fourth inlets **111-114** may include a male connector port projecting from the body **102**, each male connector port may reversibly engage a female connector coupled to a barrel of the carrier syringe or the delivery syringe **104, 116**. In one aspect, at least one of the first, second, third and fourth inlets **111-114** may include a luer connector.

[0047] In another aspect, the injection preparation device **100** may further include an injection load monitoring device **800** (shown in **FIGs. 8 and 9**) to reversibly couple to a delivery syringe **106, 108, 116**. The injection load monitoring device **800** may include a mechanical load sensor **802** having an amplifier and an electrical coupling coupled thereto for coupling to a pressure display unit; a syringe adapter **804** coupled to the mechanical load sensor, the syringe adapter having a first surface configured to engage an outward end portion of a plunger rod of a plunger rod assembly of the delivery syringe; and a finger plate **806** coupled to the mechanical load sensor. The mechanical load sensor **802** may be selected from a miniature or subminiature load cell and a piezoresistive mechanical load sensor. In an aspect, the mechanical load sensor **802** may be operable for measuring a compression load of up to about 100 lb. The mechanical load display unit **808** may display a visual alarm, an auditory alarm, or both in response to the mechanical load applied to the delivery syringe. In an aspect, the mechanical load display unit **808** may be directly coupled to the syringe adapter or finger plate as shown in **FIG. 8**. Alternatively, as depicted in **Figs. 9B** to **9E**, the pressure display unit **808** may be configured for wired or wireless communication with the mechanical load sensor **802**.

[0048] **Figs. 5** and **6** are drawings of various aspects of a transfer shield **502** that may be used when transferring the cells from a cell storage container **402** to the cell transfer syringe **204**. In an aspect, the present disclosure provides a transfer shield for use with a cell storage container **402** having an opening covered by a sterile seal capable of penetration by a hollow needle. The transfer shield **502**

may include a body having a first surface and a second surface and define an opening therethrough from the first surface to the second surface. In an aspect, the opening may have a rim. The transfer shield **502** may further include a substantially tubular projection from the first surface defining a wall surrounding the opening. In an aspect, the hollow needle may be disposed perpendicular to the first surface from within the wall. The hollow needle may be coupled to the rim of the opening and the hollow needle may have a length less than or equal to a depth of the tubular projection from the first surface. In an aspect, the body may be substantially planar. The transfer shield **502** may include a connector port projecting from the body second surface. The connector port may define a wall surrounding the opening and the connector port may engage a syringe barrel. The connector port may include a female luer port to reversibly engage a male luer-tipped syringe. The wall of the substantially tubular projection may define an opening therethrough so that the contents of the cell storage container **402** may be visible when the transfer shield **502** is in use to penetrate the seal by contacting the seal with the hollow needle. The transfer shield **502** may include a removable adhesive sterile barrier disposed over the opening through the body.

[0049] In another aspect, any combination described herein may include a cell storage container **402** and further include a prepared cell composition. The prepared cell composition may include but is not limited to cells selected from neuronal stem cells, chondrocytes, notochordal cells, chondrogenic cells, mesenchymal stem cells, hematopoietic stem cells, and any pluripotent stem cells including embryonic and induced pluripotent stem cells. The prepared cell composition may include but is not limited to mesenchymal stem cells derived from at least one of bone marrow, adipose tissue, synovium, periosteum, post-partum connective tissue, placenta, cord blood, and umbilical cord. In a non-limiting example, a prepared cell composition can comprise culture-expanded juvenile cartilage cells which are then combined for injection with a protein-based carrier such as fibrin.

[0050] A fibrin carrier may be prepared for example by combining thrombin and fibrinogen which react to form fibrin. It will be understood that once combined,

thrombin and fibrinogen react quickly to form fibrin. Thus for example the devices, systems and methods described herein can be used to conveniently combine a prepared cell composition with a fibrin carrier which is itself prepared by a combination (of thrombin and fibrinogen). In a non-limiting example, the devices, systems and methods described herein may be used to conveniently prepare and then inject NuQu® into an intervertebral disc. NuQu® is a cell-based composition of culture-expanded juvenile cartilage chondrocytes in a fibrin carrier, as described for example in U.S. Pat. No. 7,879,604, the entire disclosure of which is herein incorporated by reference.

[0051] Thus, for example, the carrier syringe **104** may include two barrels and a double-barrel plunger rod assembly **118** configured to transfer a first predetermined amount of a first carrier component and a second predetermined amount of a second carrier component. The double-barrel plunger rod assembly **118** may include a first plunger rod for slidably engaging the first barrel of the carrier syringe **104** and a second plunger rod for slidably engaging the second barrel of the carrier syringe **104**, where the first plunger rod is shorter than the second plunger rod so that the first predetermined amount of the first carrier component is less than the second predetermined amount of the second carrier component.

[0052] In an aspect, the first carrier component may be thrombin and the second carrier component may be fibrinogen, which when combined form fibrin. Other such two-component carriers can be used. Non-limiting examples of a first carrier component include thrombin, fibrinogen, poly(ethylene glycol) (PEG), poly(ethylene oxide) (PEO), poly(vinyl alcohol) (PVA), PEG–polystyrene copolymers (PEG)–(PST), polylactic acid (PLA), ethylene glycol–lactic acid copolymers, ethylene glycol–lactic acid–caprolactone copolymers, poly(d,l-lactide-*co*-ε-caprolactone), (poly)-anhydrides, anhydrides, urethanes, polysaccharides, dextran, collagen, hyaluronic acid, diethyl fumarate/poly(propylene fumarate), chitosan, a caprolactone polymer such as polycaprolactone (PCL), polyglycolic acid (PGA), or a copolymer of polylactic acid and polyglycolic acid (PLGA), and any combination thereof. In another aspect, the

first carrier component may be a photoactive polymerizing polymer. Non-limiting examples of photoactive polymerizing polymers or monomers include collagen such as high density collagen, styrene, N-vinylpyrrolidone, acrylates, epoxides, urethanes, polyethers, and polyesters. In an aspect, the first carrier component may further include a photoinitiator. In another aspect, the second carrier component may include a photoinitiator. Non-limiting examples of photoinitiators include Diazopyruvate, Rose Bengal, riboflavin, riboflavin 5-monophosphate sodium salt dehydrate, m-tetrahydroxyphenylchlorin (mTHPC), benzophenone, xanthones, quinones, benzoin ethers, acetophenones, benzoyl oximes, and acylphosphines.

[0053] In any of the devices, kits and methods described herein, a non-limiting example use of a photoactive polymerizing polymer is as follows: a first carrier component and a second component can be prepared in any way which, when the two carrier components are combined, combines a photoactive polymerizing polymer and a photinitiator. In another aspect, only a first carrier component may be used. Alternatively, the first carrier component can include both a photoactive polymerizing polymer and a photinitiator, and the second carrier component can include other materials as detailed elsewhere herein. For example the photoactive polymerizing polymer can be high density collagen (HDC) and the photoinitiator can be riboflavin. Once combined, the photoactive polymerizing polymer and photinitiator are then exposed to an appropriate wavelength of light given the selected photinitiator. For example, if HDC and riboflavin are used, once combined the HDC is photochemically cross-linked by exposure to an appropriate wavelength of light for riboflavin, about 458 nm. The resulting photochemical cross-linking of the HDC provides a gel scaffold that promotes cell viability and reduces gel contraction.

[0054] In various aspects, the first predetermined amount may be from about 0.5 cc to about 1.5 cc, from about 0.5 to about 0.7 cc, from about 0.6 cc to about 0.8 cc, from about 0.7 cc to about 0.9 cc, from about 0.8 cc to about 1.0 cc, from about 0.9 cc to about 1.1 cc, from about 1.0 cc to about 1.2 cc, from about 1.1 cc to about 1.3 cc, from about 1.2 cc to about 1.4 cc, and from about 1.3 cc to about

1.5 cc. The second predetermined amount may be from about 0.5 cc to about 1.5 cc, from about 0.5 to about 0.7 cc, from about 0.6 cc to about 0.8 cc, from about 0.7 cc to about 0.9 cc, from about 0.8 cc to about 1.0 cc, from about 0.9 cc to about 1.1 cc, from about 1.0 cc to about 1.2 cc, from about 1.1 cc to about 1.3 cc, from about 1.2 cc to about 1.4 cc, and from about 1.3 cc to about 1.5 cc. In one aspect, the first predetermined amount may be about 0.6 cc and the second predetermined amount may be about 1.1 cc.

[0055] In any of the devices, kits and methods described herein, the first carrier component, second carrier component, or cell composition may optionally include one or more growth factors, osteostimulative agents, and/or bone morphogenetic proteins, which may be obtained by prior isolation from allogenic bone. Non-limiting examples of such growth factors that may be included into a first or second carrier component or cell composition of the present teachings include a member of the TGF-β superfamily, such as TGF-β1, TGF-β2, TGF-β3, or a bone morphogenetic protein (BMP); a growth differentiation factor; ADMP-1; a fibroblast growth factor (FGF) such as acidic FGF or basic FGF; a member of the hedgehog family of proteins, such as indian hedgehog, sonic hedgehog, or desert hedgehog; a platelet-derived growth factor, an interleukin; a colony-stimulating factor; an activin; a member of the insulin-like growth factor (IGF) family, such as IGF-I or IGF-II; a member of the platelet-derived growth factor (PDGF) family, such as PDGF-AP, PDGF-BB and PDGF-AA; a member of the interleukin (IL) family, such as IL-1, IL-2, IL-3, IL-4, IL-5 or IL-6; or a member of the colony-stimulating factor (CSF) family, such as CSF-1, G-CSF, and GM-CSF. A growth factor may be a growth factor obtained from a tissue source, or can be a recombinant growth factor produced in vitro, in a cell culture, or in a microorganism using standard molecular biology techniques. In some aspects, a growth factor may be a bone morphogenetic protein, such as, in non-limiting example, BMP-1, BMP-2, BMP-3, BMP-4, BMP-5, BMP-6 or BMP-7. Any such growth factors may for example be obtained by prior isolation from bone tissue including allogenic bone tissue. For example, one or more growth factors such as one or more BMPs may be isolated

from allogenic bone and incorporated in the first carrier component, second carrier component, or cell composition.

[0056] The first carrier component, second carrier component, or cell composition as described herein may comprise, in addition to or instead of a growth factor, nutritional factors, hormones, peptides/proteins, or polysaccharides. Nutritional factors may include, but are not limited to, fatty acids, calcium, dextrose, glucose, glutamine, and vitamins such as vitamin A, B complex vitamins, vitamin C, vitamin D, vitamin E, or vitamin K. Hormones may include, but are not limited to, estrogen, testosterone, growth hormone, and thyroid hormone. Non-limiting examples of peptides or proteins include amino acids, link protein, GHK-copper peptide, BMP-13, BMP-14, PLAB, bone marrow aspirate lysate, and platelet lysate. Non-limiting examples of polysaccharides or monosaccharides includes carbohydrates, such as glucose or polymers thereof, dextran, hyaluronic acid (HyA), oligosaccharides of HyA, heparin, heparan sulfate, N-acetyl-glucosamine, and marine sulfated polysaccharides.

ii. 5-inlet Injection Preparation Device

[0057] **Figs. 2 and 3** are drawings of an injection preparation device with five inlets **200**. In one aspect, the five-inlet injection preparation device **200** includes a body **202** to reversibly engage a multi-barrel carrier syringe **104**, a cell transfer syringe **302**, a cell delivery syringe **106** and a carrier delivery syringe **108**, the body **202** including a first transfer portion defining a first inlet **211** to reversibly couple to a first barrel of the multi-barrel carrier syringe **104**, a second inlet **212** to reversibly couple to the barrel of the cell delivery syringe **106**, and a fifth inlet **215** to reversibly couple to the barrel of the cell transfer syringe **204**, and a second transfer portion defining a third inlet **213** to reversibly couple to a second barrel of the multi-barrel carrier syringe **104**, a fourth inlet **214** to reversibly couple to the barrel of the carrier delivery syringe **108**. The first, second, and fifth inlets **211, 212, 215** communicate through a first conduit through the body **202** and the third and fourth inlets **213, 214** communicate through a second conduit through the body **202**. At least one of the first, second, third, fourth and fifth inlets **211-215** may

include a female connector port projecting from the body **202**, where each female connector port may receive the injection end of a barrel of the carrier syringe **104** or the delivery syringe **106, 108**. At least one of the first, second, third, fourth and fifth inlets **211-215** may include a male connector port projecting from the body **202**, where each male connector port may reversibly engage a female connector coupled to a barrel of the carrier syringe **104** or the delivery syringe **106, 108**. In an aspect, at least one of the first, second, third, fourth and fifth inlets **211-215** may include a luer connector. In an aspect, the first transfer portion may include a two-way valve to limit a fluid path between the first and second inlets **211, 212** or between the first and fifth inlets **211, 215**. In another aspect, the third inlet **213** defined by the second transfer portion may include a one-way valve.

[0058] In another aspect, as illustrated in **Figs. 2** and **3**, the present disclosure provides a five-inlet injection preparation device **200**, the cell delivery syringe **106** and the carrier delivery syringe **108** may be multiple barrels of a multi-barrel delivery syringe **116**. This aspect may include a body **202** adapted to reversibly couple to a multi-barrel carrier syringe **104**, a multi-barrel delivery syringe **116** and a cell transfer syringe **204**, the body **202** having a first transfer portion defining a first inlet **211** to reversibly couple to a first barrel of the multi-barrel carrier syringe **104**, a second inlet **212** to reversibly couple to a first barrel of the multi-barrel delivery syringe **116**, and a fifth inlet **215** to reversibly couple to the cell transfer syringe **204**, and a second transfer portion defining a third inlet **213** configured to reversibly couple to a second barrel of the multi-barrel carrier syringe **104**, and a fourth inlet **214** configured to reversibly couple to a second barrel of the multi-barrel delivery syringe **116**. The first inlet, second inlet and fifth inlet **211, 212, 215** communicate through a first conduit through the body **202** and the third and fourth inlets **213, 214** communicate through a second conduit through the body **202**. At least one of the first, second, third, fourth and fifth inlets **211-215** may include a female connector port projecting from the body **202**, where each female connector port may receive the injection end of a barrel of one of the carrier, delivery or cell transfer syringes **104, 116, 204**. At least one of the first, second, third, fourth and fifth inlets **211-215** may include a male connector

port projecting from the body **202**, each male connector port may reversibly engage a female connector coupled to a barrel of the carrier syringe **104** or the delivery syringe **116**. In one aspect, at least one of the first, second, third, fourth and fifth inlets **211-215** may be a luer connector. The first transfer portion may include a two-way valve to limit a fluid path between the first and second inlets **211, 212** or between the first and fifth inlets **211, 215**. The second inlet **212** defined by the second transfer portion may include a one-way valve.

[0059] In another aspect, the injection preparation device **100** may further include an injection load monitoring device **800** (shown in **FIGs. 8 and 9**) to reversibly couple to a delivery syringe **106, 108, 116**. The injection load monitoring device **800** may include a mechanical load sensor **802** having an amplifier and an electrical coupling coupled thereto for coupling to a pressure display unit; a syringe adapter **804** coupled to the mechanical load sensor, the syringe adapter having a first surface configured to engage an outward end portion of a plunger rod of a plunger rod assembly of the delivery syringe; and a finger plate **806** coupled to the mechanical load sensor. The mechanical load sensor **802** may be selected from a miniature or subminiature load cell and a piezoresistive mechanical load sensor. In an aspect, the mechanical load sensor **802** may be operable for measuring a compression load of up to about 100 lb. The mechanical load display unit **808** may display a visual alarm, an auditory alarm, or both in response to the mechanical load applied to the delivery syringe. In an aspect, the mechanical load display unit **808** may be directly coupled to the syringe adapter or finger plate as shown in **FIG. 8**. Alternatively, as depicted in **Figs. 9B** to **9E**, the pressure display unit **808** may be configured for wired or wireless communication with the mechanical load sensor **802**.

[0060] **Figs. 5** and **6** are drawings of various aspects of a transfer shield **502** that may be used when transferring the cells from a cell storage container **402** to the cell transfer syringe **204**. In an aspect, the present disclosure provides a transfer shield for use with a cell storage container **402** having an opening covered by a sterile seal capable of penetration by a hollow needle. The transfer shield **502** may include a body having a first surface and a second surface and define an

opening therethrough from the first surface to the second surface. In an aspect, the opening may have a rim. The transfer shield **502** may further include a substantially tubular projection from the first surface defining a wall surrounding the opening. In an aspect, the hollow needle may be disposed perpendicular to the first surface from within the wall. The hollow needle may be coupled to the rim of the opening and the hollow needle may have a length less than or equal to a depth of the tubular projection from the first surface. In an aspect, the body may be substantially planar. The transfer shield **502** may include a connector port projecting from the body second surface. The connector port may define a wall surrounding the opening and the connector port may engage a syringe barrel. The connector port may include a female luer port to reversibly engage a male luer-tipped syringe. The wall of the substantially tubular projection may define an opening therethrough so that the contents of the cell storage container **402** may be visible when the transfer shield **502** is in use to penetrate the seal by contacting the seal with the hollow needle. The transfer shield **502** may include a removable adhesive sterile barrier disposed over the opening through the body.

[0061] In another aspect, any combination described herein may include a cell storage container **402** and further include a prepared cell composition. The prepared cell composition may include but is not limited to cells selected from neuronal stem cells, chondrocytes, notochordal cells, chondrogenic cells, mesenchymal stem cells, hematopoietic stem cells, and any pluripotent stem cells including embryonic and induced pluripotent stem cells. The prepared cell composition may include but is not limited to mesenchymal stem cells derived from at least one of bone marrow, adipose tissue, synovium, periosteum, post-partum connective tissue, placenta, cord blood, and umbilical cord. In a non-limiting example, a prepared cell composition can comprise culture-expanded juvenile cartilage cells which are then combined for injection with a protein-based carrier such as fibrin.

[0062] In an aspect, the carrier syringe **104** may include two barrels and a double-barrel plunger rod assembly **118** configured to transfer a first predetermined amount of a first carrier component and a second predetermined

amount of a second carrier component. The double-barrel plunger rod assembly **118** may include a first plunger rod for slidably engaging the first barrel of the carrier syringe **104** and a second plunger rod for slidably engaging the second barrel of the carrier syringe **104**, where the first plunger rod is shorter than the second plunger rod so that the first predetermined amount of the first carrier component is less than the second predetermined amount of the second carrier component.

[0063] In an aspect, the first carrier component may be thrombin and the second carrier component may be fibrinogen. Non-limiting examples of the first carrier component include thrombin, fibrinogen, poly(ethylene glycol) (PEG), poly(ethylene oxide) (PEO), poly(vinyl alcohol) (PVA), PEG–polystyrene copolymers (PEG)–(PST), polylactic acid (PLA), ethylene glycol–lactic acid copolymers, ethylene glycol–lactic acid–caprolactone copolymers, poly(d,l-lactide-*co*-ε-caprolactone), (poly)-anhydrides, anhydrides, urethanes, polysaccharides, dextran, collagen, hyaluronic acid, diethyl fumarate/poly(propylene fumarate), chitosan, a caprolactone polymer such as polycaprolactone (PCL), polyglycolic acid (PGA), or a copolymer of polylactic acid and polyglycolic acid (PLGA), and any combination thereof. In another aspect, the first carrier component may be a photoactive polymerizing polymer. Non-limiting examples of photoactive polymerizing polymers or monomers include collagen such as high density collagen, styrene, N-Vinylpyrrolidone, acrylates, epoxides, urethanes, polyethers, and polyesters. In an aspect, the first carrier component may further include a photoinitiator. In another aspect, the second carrier component may include a photoinitiator. Non-limiting examples of photoinitiators include Diazopyruvate, Rose Bengal, riboflavin, riboflavin 5-monophosphate sodium salt dehydrate, m-tetrahydroxyphenylchlorin (mTHPC), benzophenone, xanthones, quinones, benzoin ethers, acetophenones, benzoyl oximes, and acylphosphines.

[0064] In any of the devices, kits and methods described herein, a non-limiting example use of a photoactive polymerizing polymer is as follows: a first carrier component and a second component can be prepared in any way

which, when the two carrier components are combined, combines a photoactive polymerizing polymer and a photinitiator. In another aspect, only a first carrier component may be used. Alternatively, the first carrier component can include both a photoactive polymerizing polymer and a photinitiator, and the second carrier component can include other materials as detailed elsewhere herein. For example the photoactive polymerizing polymer can be high density collagen (HDC) and the photoinitiator can be riboflavin. Once combined, the photoactive polymerizing polymer and photinitiator are then exposed to an appropriate wavelength of light given the selected photinitiator. For example, if HDC and riboflavin are used, once combined the HDC is photochemically cross-linked by exposure to an appropriate wavelength of light for riboflavin, about 458 nm. The resulting photochemical cross-linking of the HDC provides a gel scaffold that promotes cell viability and reduces gel contraction.

[0065] In various aspects, the first predetermined amount may be from about 0.5 cc to about 1.5 cc, from about 0.5 to about 0.7 cc, from about 0.6 cc to about 0.8 cc, from about 0.7 cc to about 0.9 cc, from about 0.8 cc to about 1.0 cc, from about 0.9 cc to about 1.1 cc, from about 1.0 cc to about 1.2 cc, from about 1.1 cc to about 1.3 cc, from about 1.2 cc to about 1.4 cc, and from about 1.3 cc to about 1.5 cc. The second predetermined amount may be from about 0.5 cc to about 1.5 cc, from about 0.5 to about 0.7 cc, from about 0.6 cc to about 0.8 cc, from about 0.7 cc to about 0.9 cc, from about 0.8 cc to about 1.0 cc, from about 0.9 cc to about 1.1 cc, from about 1.0 cc to about 1.2 cc, from about 1.1 cc to about 1.3 cc, from about 1.2 cc to about 1.4 cc, and from about 1.3 cc to about 1.5 cc. In one aspect, the first predetermined amount may be about 0.6 cc and the second predetermined amount may be about 1.1 cc.

[0066] In any of the devices, kits and methods described herein, the first carrier component, second carrier component, or cell composition may optionally include one or more growth factors, osteostimulative agents, and/or bone morphogenetic proteins, which may be obtained by prior isolation from allogenic bone. Non-limiting examples of such growth factors that may be included into a first or second carrier component or cell composition of the present teachings

include a member of the TGF-β superfamily, such as TGF-β1, TGF-β2, TGF-β3, or a bone morphogenetic protein (BMP); a growth differentiation factor; ADMP-1; a fibroblast growth factor (FGF) such as acidic FGF or basic FGF; a member of the hedgehog family of proteins, such as indian hedgehog, sonic hedgehog, or desert hedgehog; a platelet-derived growth factor, an interleukin; a colony-stimulating factor; an activin; a member of the insulin-like growth factor (IGF) family, such as IGF-I or IGF-II; a member of the platelet-derived growth factor (PDGF) family, such as PDGF-AP, PDGF-BB and PDGF-AA; a member of the interleukin (IL) family, such as IL-1, IL-2, IL-3, IL-4, IL-5 or IL-6; or a member of the colony-stimulating factor (CSF) family, such as CSF-1, G-CSF, and GM-CSF. A growth factor may be a growth factor obtained from a tissue source, or can be a recombinant growth factor produced in vitro, in a cell culture, or in a microorganism using standard molecular biology techniques. In some aspects, a growth factor may be a bone morphogenetic protein, such as, in non-limiting example, BMP-1, BMP-2, BMP-3, BMP-4, BMP-5, BMP-6 or BMP-7. Any such growth factors may for example be obtained by prior isolation from bone tissue including allogenic bone tissue. For example, one or more growth factors such as one or more BMPs may be isolated from allogenic bone and incorporated in the first carrier component, second carrier component, or cell composition.

[0067] The first carrier component, second carrier component, or cell composition as described herein may comprise, in addition to or instead of a growth factor, nutritional factors, hormones, peptides/proteins, or polysaccharides. Nutritional factors may include, but are not limited to, fatty acids, calcium, dextrose, glucose, glutamine, and vitamins such as vitamin A, B complex vitamins, vitamin C, vitamin D, vitamin E, or vitamin K. Hormones may include, but are not limited to, estrogen, testosterone, growth hormone, and thyroid hormone. Non-limiting examples of peptides or proteins include amino acids, link protein, GHK-copper peptide, BMP-13, BMP-14, PLAB, bone marrow aspirate lysate, and platelet lysate. Non-limiting examples of polysaccharides or monosaccharides includes carbohydrates, such as glucose or polymers thereof, dextran, hyaluronic acid

(HyA), oligosaccharides of HyA, heparin, heparan sulfate, N-acetyl-glucosamine, and marine sulfated polysaccharides.

B. Injection Preparation Kits

i. 4-inlet Injection Preparation Kit

[0068] In various aspects, the present disclosure provides an injection preparation kit including the four-inlet injection preparation device **100** described herein above, and at least one of a multi-barrel carrier syringe **104**, a cell transfer syringe **204**, a cell delivery syringe **106** and a carrier delivery syringe **108**. At least one or more of the multi-barrel carrier syringe **104**, cell transfer syringe **204**, cell delivery syringe **106** and carrier delivery syringe **108** may be coupled to the body **102**. In one aspect, the multi-barrel carrier syringe **104**, cell delivery syringe **106** and carrier delivery syringe **108** may be coupled to the body **102**. The carrier syringe **104** may include two barrels and a double-barrel plunger rod assembly **118** to transfer a first predetermined amount of a first carrier component and a second predetermined amount of a second carrier component. In an aspect, the kit may include the cell delivery syringe **106** and the carrier delivery syringe **108** or the cell transfer syringe **204**. In one aspect, the cell transfer syringe **204** may be a single-barrel syringe.

[0069] In another aspect, the present disclosure provides an injection preparation kit including the four-inlet injection preparation device **100** described herein above, and at least one of the multi-barrel carrier syringe **104**, the multi-barrel delivery syringe **116** and the cell transfer syringe **204**. At least one or more of the multi-barrel carrier syringe **104**, the multi-barrel delivery syringe **116** and the cell transfer syringe **204** may be coupled to the body **102**. In one aspect, the multi-barrel carrier syringe **104** and the multi-barrel delivery syringe **116** may be coupled to the body **102**. In another aspect, the multi-barrel delivery syringe **116** and the cell transfer syringe **204** may be coupled to the body. The multi-barrel delivery syringe **116** may include two barrels and a double-barrel plunger rod assembly. In an aspect, the injection preparation kit may include the multi-barrel

delivery syringe **116** or the cell transfer syringe **204**. In one aspect, the cell transfer syringe **204** may be a single-barrel syringe.

[0070] In another aspect, the present disclosure provides for an injection preparation kit for transferring a prepared cell composition from a cell storage container **402** to a cell transfer syringe **204**. The injection preparation kit may include at least the injection preparation device **100** described herein above and a transfer shield **502**. The injection preparation kit may include a cell storage container **402** including a substantially cylindrical body defining a central lumen, a first end and a second end. The first end may define a vent port and a fill port, and the second end may define an access port. In an aspect, a flexible sealing element may be over the access port. The vent port, fill port and access port may communicate with the central lumen. The injection preparation kit may include a cell storage container **402** including a substantially cylindrical body defining a central lumen, a first end and a second end. There the first end may define a fill opening, and the second end may define an access port. In an aspect, a flexible sealing element may be over the access port. The cell storage container **402** may further include a cap configured to seal the fill opening, where the fill opening and access port communicate with the central lumen. The flexible sealing element may include a rubber septum. The cell storage container **402** may have an inner surface and an outer surface, where the inner surface may be sterile and the outer surface may be non-sterile. The cell storage container **402** may contain a prepared cell composition for transfer to a delivery syringe. The second end may further define a connector port for reversibly engaging a connector port of a second device. In an aspect, the cell storage container **402** may operate with an automated filling machine.

[0071] In an aspect, the injection preparation kit may further include a Y-connector **700** to reversibly couple to a multi-barrel delivery syringe **116**. The Y-connector may include a connector body **702** having a first end and a second end, the first end defining at least two connector inlets for reversibly coupling the Y-connector to the at least two barrels of the delivery syringe **116.** The Y-connector may further include a dual lumen cannula **704** coupled to the second end of the

connector body. In an aspect, a spinal needle may be coupled to the dual lumen cannula **704**.

[0072] In an aspect, the injection preparation kit may further include a light source or light conduit, such as an optic fiber, to expose a photoactivated polymer(s) at or near the end of the dual lumen cannula **704**. In one aspect, the light source and/or light conduit may run the length of the dual lumen cannula **704**. In various aspects, the light source and/or light conduit may be integral or attached to the Y-connector **700**, dual lumen cannula **704**, spinal needle, or delivery syringe **116**. During the repair of tissue it may be desired to use a light polymerizing polymer as a carrier component for the delivery of biologic cells or drugs. The advantage in this arrangement is a single carrier component with the mixed in biologic cells or drugs may be sufficient instead of needing a two part carrier that reacts together. In an aspect, the carrier component may be polymerized by light which may be delivered via an integrated fiber optic in or on the spinal needle. This may allow for a rapid hardening of the photoactive polymer so it does not migrate and provide structural support similar to the current properties of the disc annulus. It also may allow for the contouring of the repair by controlled delivery and hardening of the polymer. In another aspect, using a light source with a photoactive polymer may allow for the construction of geometric structures to fit the deflect shape.

[0073] In one aspect, the injection preparation kit may include a fiber optic endoscope through which the spinal needle may be passed. The endoscope may allow for illumination and viewing of the defects repair which may allow for the contouring (geometric construction) of the polymerized carrier component with mixed in biologic cells or drugs.

[0074] In another aspect, even if the carrier is multi-component and delivered via a multi-barrel delivery syringe **116**, the polymerization rate of the delivered polymer may be 'tuned' via light intensity. In one aspect, the fiber optic may be integrated into the delivery syringe **116** with the polymer being exposed to the light at the syringe hub to spinal needle transition. In another aspect, the fiber optic may be integrated into the dual lumen cannula **704**. In either aspect, this

would initiate the reaction for polymer polymerization before the carrier component(s) enter the needle and thus would be reacting as it is progressing down the needle to be delivered. This may have the benefit of allowing for a lower profile (outer diameter) spinal needle for delivery.

[0075] In another aspect, the present disclosure provides a transfer shield **502** for use with a cell storage container **402** having an opening covered by a sterile seal capable of penetration by a hollow needle. The transfer shield **502** may include a body having a first surface and a second surface and define an opening therethrough from the first surface to the second surface, the opening having a rim. The transfer shield **502** may further include a substantially tubular projection from the first surface defining a wall surrounding the opening. The hollow needle may be disposed perpendicular to the first surface from within the wall. In an aspect, the hollow needle may be coupled to the rim of the opening and the hollow needle may have a length less than or equal to a depth of the tubular projection from the first surface. In an aspect, the body of the transfer shield **502** may be substantially planar. The transfer shield **502** may include a connector port projecting from the body second surface, where the connector port defines a wall surrounding the opening and where the connector port may engage a syringe barrel. The connector port may include a female luer port to reversibly engage a male luer-tipped syringe. The wall of the substantially tubular projection may define an opening therethrough so that the contents of the cell storage container may be visible when the shield is in use to penetrate the seal by contacting the seal with the hollow needle. The transfer shield **502** may include a removable adhesive sterile barrier disposed over the opening through the body.

[0076] In an aspect, the injection preparation kit may include an amount of the cell preparation. In another aspect, the present disclosure provides an injection preparation kit described herein further including an amount of at least a first carrier component. The kit may further include an amount of a second carrier component, where the amounts of the first and the second carrier components are packaged separately. The first and the second carrier components when combined may form a polymerized hydrogel.

[0077] In an aspect, the injection preparation kit may include the cell storage container **402** and further include a prepared cell composition. The prepared cell composition may include but is not limited to cells selected from neuronal stem cells, chondrocytes, notochordal cells, chondrogenic cells, mesenchymal stem cells, hematopoietic stem cells, and any pluripotent stem cells including embryonic and induced pluripotent stem cells. The prepared cell composition may include but is not limited to mesenchymal stem cells derived from at least one of bone marrow, adipose tissue, synovium, periosteum, post-partum connective tissue, placenta, cord blood, and umbilical cord.

[0078] In an aspect, the carrier syringe **104** may include two barrels and a double-barrel plunger rod assembly **118** configured to transfer a first predetermined amount of a first carrier component and a second predetermined amount of a second carrier component. The double-barrel plunger rod assembly **118** may include a first plunger rod for slidably engaging the first barrel of the carrier syringe and a second plunger rod for slidably engaging the second barrel of the carrier syringe, where the first plunger rod is shorter than the second plunger rod so that the first predetermined amount of the first carrier component is less than the second predetermined amount of the second carrier component.

[0079] In an aspect, the first carrier component may be thrombin and the second carrier component may be fibrinogen. Non-limiting examples of the first carrier component include thrombin, fibrinogen, poly(ethylene glycol) (PEG), poly(ethylene oxide) (PEO), poly(vinyl alcohol) (PVA), PEG–polystyrene copolymers (PEG)–(PST), polylactic acid (PLA), ethylene glycol–lactic acid copolymers, ethylene glycol–lactic acid–caprolactone copolymers, poly(d,l-lactide-*co*-ε-caprolactone), (poly)-anhydrides, anhydrides, urethanes, polysaccharides, dextran, collagen, hyaluronic acid, diethyl fumarate/poly(propylene fumarate), chitosan, a caprolactone polymer such as polycaprolactone (PCL), polyglycolic acid (PGA), or a copolymer of polylactic acid and polyglycolic acid (PLGA), and combinations thereof. In another aspect, the first carrier component may be a photoactive polymerizing polymer. Non-limiting examples of photoactive polymerizing polymers or monomers include collagen,

styrene, N-Vinylpyrrolidone, acrylates, epoxides, urethanes, polyethers, and polyesters. In an aspect, the first carrier component may further include a photoinitiator. In another aspect, the second carrier component may include a photoinitiator. Non-limiting examples of photoinitiators include Diazopyruvate, Rose Bengal, riboflavin, riboflavin 5-monophosphate sodium salt dehydrate, m-tetrahydroxyphenylchlorin (mTHPC), benzophenone, xanthones, quinones, benzoin ethers, acetophenones, benzoyl oximes, and acylphosphines.

[0080] In various aspects, the first predetermined amount may be from about 0.5 cc to about 1.5 cc, from about 0.5 to about 0.7 cc, from about 0.6 cc to about 0.8 cc, from about 0.7 cc to about 0.9 cc, from about 0.8 cc to about 1.0 cc, from about 0.9 cc to about 1.1 cc, from about 1.0 cc to about 1.2 cc, from about 1.1 cc to about 1.3 cc, from about 1.2 cc to about 1.4 cc, and from about 1.3 cc to about 1.5 cc. The second predetermined amount may be from about 0.5 cc to about 1.5 cc, from about 0.5 to about 0.7 cc, from about 0.6 cc to about 0.8 cc, from about 0.7 cc to about 0.9 cc, from about 0.8 cc to about 1.0 cc, from about 0.9 cc to about 1.1 cc, from about 1.0 cc to about 1.2 cc, from about 1.1 cc to about 1.3 cc, from about 1.2 cc to about 1.4 cc, and from about 1.3 cc to about 1.5 cc. In one aspect, the first predetermined amount may be about 0.6 cc and the second predetermined amount may be about 1.1 cc.

[0081] In any of the devices, kits and methods described herein, the first carrier component, second carrier component, or cell composition may optionally include one or more growth factors, osteostimulative agents, and/or bone morphogenetic proteins, which may be obtained by prior isolation from allogenic bone. Non-limiting examples of such growth factors that may be included into a first or second carrier component or cell composition of the present teachings include a member of the TGF-β superfamily, such as TGF-β1, TGF-β2, TGF-β3, or a bone morphogenetic protein (BMP); a growth differentiation factor; ADMP-1; a fibroblast growth factor (FGF) such as acidic FGF or basic FGF; a member of the hedgehog family of proteins, such as indian hedgehog, sonic hedgehog, or desert hedgehog; a platelet-derived growth factor, an interleukin; a colony-stimulating factor; an activin; a member of the insulin-like growth factor (IGF) family, such as

IGF-I or IGF-II; a member of the platelet-derived growth factor (PDGF) family, such as PDGF-AP, PDGF-BB and PDGF-AA; a member of the interleukin (IL) family, such as IL-1, IL-2, IL-3, IL-4, IL-5 or IL-6; or a member of the colony-stimulating factor (CSF) family, such as CSF-1, G-CSF, and GM-CSF. A growth factor may be a growth factor obtained from a tissue source, or can be a recombinant growth factor produced in vitro, in a cell culture, or in a microorganism using standard molecular biology techniques. In some aspects, a growth factor may be a bone morphogenetic protein, such as, in non-limiting example, BMP-1, BMP-2, BMP-3, BMP-4, BMP-5, BMP-6 or BMP-7. Any such growth factors may for example be obtained by prior isolation from bone tissue including allogenic bone tissue. For example, one or more growth factors such as one or more BMPs may be isolated from allogenic bone and incorporated in the first carrier component, second carrier component, or cell composition.

[0082] The first carrier component, second carrier component, or cell composition as described herein may comprise, in addition to or instead of a growth factor, nutritional factors, hormones, peptides/proteins, or polysaccharides. Nutritional factors may include, but are not limited to, fatty acids, calcium, dextrose, glucose, glutamine, and vitamins such as vitamin A, B complex vitamins, vitamin C, vitamin D, vitamin E, or vitamin K. Hormones may include, but are not limited to, estrogen, testosterone, growth hormone, and thyroid hormone. Non-limiting examples of peptides or proteins include amino acids, link protein, GHK-copper peptide, BMP-13, BMP-14, PLAB, bone marrow aspirate lysate, and platelet lysate. Non-limiting examples of polysaccharides or monosaccharides includes carbohydrates, such as glucose or polymers thereof, dextran, hyaluronic acid (HyA), oligosaccharides of HyA, heparin, heparan sulfate, N-acetyl-glucosamine, and marine sulfated polysaccharides.

ii. 5-inlet Injection Preparation Kit

[0083] In various aspects, the present disclosure provides an injection preparation kit including the five-inlet injection preparation device **200** described herein above, and at least one of a multi-barrel carrier syringe **104**, a cell transfer

syringe **204**, a cell delivery syringe **106** and a carrier delivery syringe **108**. At least one or more of the multi-barrel carrier syringe **104**, cell transfer syringe **204**, cell delivery syringe **106** and carrier delivery syringe **108** may be coupled to the body **202**. In one aspect, the multi-barrel carrier syringe **104**, cell delivery syringe **106** and carrier delivery syringe **108** may be coupled to the body **202**. The injection preparation kit may include the multi-barrel carrier syringe **104**. The carrier syringe **104** may include two barrels and a double-barrel plunger rod assembly **118** to transfer a first predetermined amount of a first carrier component and a second predetermined amount of a second carrier component. In an aspect, the kit may include the cell delivery syringe **106** and the carrier delivery syringe **108** or the cell transfer syringe **204**. In one aspect, the cell transfer syringe **204** may be a single-barrel syringe.

[0084] In another aspect, the present disclosure provides an injection preparation kit including the five-inlet injection preparation device **200** described herein above and at least one of the multi-barrel carrier syringe **104**, the multi-barrel delivery syringe **116** and the cell transfer syringe **204**. At least one or more of the multi-barrel carrier syringe **104**, the multi-barrel delivery syringe **116** and the cell transfer syringe **204** may be coupled to the body **202**. In one aspect, the multi-barrel carrier syringe **104** and the multi-barrel delivery syringe **116** may be coupled to the body **202**. In another aspect, the multi-barrel delivery syringe **116** and the cell transfer syringe **204** may be coupled to the body. The injection preparation kit may include the multi-barrel delivery syringe **116**, where the delivery syringe **116** includes two barrels and a double-barrel plunger rod assembly. In an aspect, the injection preparation kit may include the cell transfer syringe **204**. In one aspect, the cell transfer syringe **204** may be a single-barrel syringe.

[0085] In another aspect, the present disclosure provides for an injection preparation kit for transferring a prepared cell composition from a cell storage container **402** to a cell transfer syringe **204**. The injection preparation kit may include at least the injection preparation device **200** described herein above and a transfer shield **502**. The injection preparation kit may include a cell storage

container **402** including a substantially cylindrical body defining a central lumen, a first end and a second end. The first end may define a vent port and a fill port, and the second end may define an access port, where a flexible sealing element may be over the access port. In an aspect, the vent port, fill port and access port communicate with the central lumen. The injection preparation kit may include a cell storage container **402** including a substantially cylindrical body defining a central lumen, a first end and a second end. The first end may define a fill opening, and the second end may define an access port and a flexible sealing element over the access port. A cap may be configured to seal the fill opening. In an aspect, the fill opening and access port communicate with the central lumen. The flexible sealing element may include a rubber septum. The cell storage container **402** may have an inner surface and an outer surface, where the inner surface may be sterile and the outer surface may be non-sterile. The cell storage container **402** may further contain a prepared cell composition for transfer to a delivery syringe. The second end may further define a connector port for reversibly engaging a connector port of a second device. In an aspect, the cell storage container **402** may operate with an automated filling machine.

[0086] In an aspect, the injection preparation kit may further include a Y-connector **700** to reversibly couple to a multi-barrel delivery syringe **116**. The Y-connector may include a connector body **702** having a first end and a second end, the first end defining at least two connector inlets for reversibly coupling the Y-connector to the at least two barrels of the delivery syringe **116**; a dual lumen cannula **704** coupled to the second end of the connector body; and a spinal needle coupled to the dual lumen cannula **704**.

[0087] In an aspect, the injection preparation kit may further include a light source or light conduit, such as an optic fiber, to expose a photoactivated polymer(s) at or near the end of the dual lumen cannula **704**. In one aspect, the light source and/or light conduit may run the length of the dual lumen cannula **704**. In various aspects, the light source and/or light conduit may be integral or attached to the Y-connector **700**, dual lumen cannula **704**, spinal needle, or delivery syringe **116**. During the repair of tissue it may be desired to use a light polymerizing

polymer as a carrier component for the delivery of biologic cells or drugs. The advantage in this arrangement is a single carrier component with the mixed in biologic cells or drugs may be sufficient instead of needing a two part carrier that reacts together. In an aspect, the carrier component may be polymerized by light which may be delivered via an integrated fiber optic in or on the spinal needle. This may allow for a rapid hardening of the photoactive polymer so it does not migrate and provide structural support similar to the current properties of the disc annulus. It also may allow for the contouring of the repair by controlled delivery and hardening of the polymer. In another aspect, using a light source with a photoactive polymer may allow for the construction of geometric structures to fit the deflect shape.

[0088] In one aspect, the injection preparation kit may include a fiber optic endoscope through which the spinal needle may be passed. The endoscope may allow for illumination and viewing of the defects repair which may allow for the contouring (geometric construction) of the polymerized carrier component with mixed in biologic cells or drugs.

[0089] In another aspect, even if the carrier is multi-component and delivered via a multi-barrel delivery syringe **116**, the polymerization rate of the delivered polymer may be 'tuned' via light intensity. In one aspect, the fiber optic may be integrated into the delivery syringe **116** with the polymer being exposed to the light at the syringe hub to spinal needle transition. In another aspect, the fiber optic may be integrated into the dual lumen cannula **704**. In either aspect, this would initiate the reaction for polymer polymerization before the carrier component(s) enter the needle and thus would be reacting as it is progressing down the needle to be delivered. This may have the benefit of allowing for a lower profile (outer diameter) spinal needle for delivery.

[0090] In another aspect, the present disclosure provides a transfer shield **502** for use with a cell storage container **402** having an opening covered by a sterile seal capable of penetration by a hollow needle. The transfer shield **502** may include a body having a first surface and a second surface and define an opening therethrough from the first surface to the second surface, the opening having a rim.

The transfer shield **502** may further include a substantially tubular projection from the first surface defining a wall surrounding the opening. The hollow needle may be disposed perpendicular to the first surface from within the wall. In an aspect, the hollow needle may be coupled to the rim of the opening and the hollow needle may have a length less than or equal to a depth of the tubular projection from the first surface. In an aspect, the body of the transfer shield **502** may be substantially planar. The transfer shield **502** may include a connector port projecting from the body second surface, where the connector port defines a wall surrounding the opening and where the connector port may engage a syringe barrel. The connector port may include a female luer port to reversibly engage a male luer-tipped syringe. The wall of the substantially tubular projection may define an opening therethrough so that the contents of the cell storage container may be visible when the shield is in use to penetrate the seal by contacting the seal with the hollow needle. The transfer shield **502** may include a removable adhesive sterile barrier disposed over the opening through the body.

[0091] In an aspect, the injection preparation kit may further include an amount of the prepared cell composition. In another aspect, the present disclosure provides an injection preparation kit described herein further including an amount of at least a first carrier component. The kit may further including an amount of a second carrier component, where the amounts of the first and the second carrier components are packaged separately. The first and the second carrier components when combined form a polymerized hydrogel.

[0092] In an aspect, the injection preparation kit may include the cell storage container **402** and further include a prepared cell composition. The prepared cell composition may include but is not limited to cells selected from neuronal stem cells, chondrocytes, notochordal cells, chondrogenic cells, mesenchymal stem cells, hematopoietic stem cells, and any pluripotent stem cells including embryonic and induced pluripotent stem cells. The prepared cell composition may include but is not limited to mesenchymal stem cells derived from at least one of bone marrow, adipose tissue, synovium, periosteum, post-partum connective tissue, placenta, cord blood, and umbilical cord.

[0093] In an aspect, the carrier syringe **104** may include two barrels and a double-barrel plunger rod assembly **118** configured to transfer a first predetermined amount of a first carrier component and a second predetermined amount of a second carrier component. The double-barrel plunger rod assembly **118** may include a first plunger rod for slidably engaging the first barrel of the carrier syringe and a second plunger rod for slidably engaging the second barrel of the carrier syringe, where the first plunger rod is shorter than the second plunger rod so that the first predetermined amount of the first carrier component is less than the second predetermined amount of the second carrier component.

[0094] In an aspect, the first carrier component may be thrombin and the second carrier component may be fibrinogen. Non-limiting examples of the first carrier component include thrombin, fibrinogen, poly(ethylene glycol) (PEG), poly(ethylene oxide) (PEO), poly(vinyl alcohol) (PVA), PEG–polystyrene copolymers (PEG)–(PST), polylactic acid (PLA), ethylene glycol–lactic acid copolymers, ethylene glycol–lactic acid–caprolactone copolymers, poly(d,l-lactide-*co*-ε-caprolactone), (poly)-anhydrides, anhydrides, urethanes, polysaccharides, dextran, collagen, hyaluronic acid, diethyl fumarate/poly(propylene fumarate), chitosan, a caprolactone polymer such as polycaprolactone (PCL), polyglycolic acid (PGA), or a copolymer of polylactic acid and polyglycolic acid (PLGA), and combinations thereof. In another aspect, the first carrier component may be a photoactive polymerizing polymer. Non-limiting examples of photoactive polymerizing polymers or monomers include collagen, styrene, N-Vinylpyrrolidone, acrylates, epoxides, urethanes, polyethers, and polyesters. In an aspect, the first carrier component may further include a photoinitiator. In another aspect, the second carrier component may include a photoinitiator. Non-limiting examples of photoinitiators include Diazopyruvate, Rose Bengal, riboflavin, riboflavin 5-monophosphate sodium salt dehydrate, m-tetrahydroxyphenylchlorin (mTHPC), benzophenone, xanthones, quinones, benzoin ethers, acetophenones, benzoyl oximes, and acylphosphines.

[0095] In various aspects, the first predetermined amount may be from about 0.5 cc to about 1.5 cc, from about 0.5 to about 0.7 cc, from about 0.6 cc to

about 0.8 cc, from about 0.7 cc to about 0.9 cc, from about 0.8 cc to about 1.0 cc, from about 0.9 cc to about 1.1 cc, from about 1.0 cc to about 1.2 cc, from about 1.1 cc to about 1.3 cc, from about 1.2 cc to about 1.4 cc, and from about 1.3 cc to about 1.5 cc. The second predetermined amount may be from about 0.5 cc to about 1.5 cc, from about 0.5 to about 0.7 cc, from about 0.6 cc to about 0.8 cc, from about 0.7 cc to about 0.9 cc, from about 0.8 cc to about 1.0 cc, from about 0.9 cc to about 1.1 cc, from about 1.0 cc to about 1.2 cc, from about 1.1 cc to about 1.3 cc, from about 1.2 cc to about 1.4 cc, and from about 1.3 cc to about 1.5 cc. In one aspect, the first predetermined amount may be about 0.6 cc and the second predetermined amount may be about 1.1 cc.

[0096] In any of the devices, kits and methods described herein, the first carrier component, second carrier component, or cell composition may optionally include one or more growth factors, osteostimulative agents, and/or bone morphogenetic proteins, which may be obtained by prior isolation from allogenic bone. Non-limiting examples of such growth factors that may be included into a first or second carrier component or cell composition of the present teachings include a member of the TGF-β superfamily, such as TGF-β1, TGF-β2, TGF-β3, or a bone morphogenetic protein (BMP); a growth differentiation factor; ADMP-1; a fibroblast growth factor (FGF) such as acidic FGF or basic FGF; a member of the hedgehog family of proteins, such as indian hedgehog, sonic hedgehog, or desert hedgehog; a platelet-derived growth factor, an interleukin; a colony-stimulating factor; an activin; a member of the insulin-like growth factor (IGF) family, such as IGF-I or IGF-II; a member of the platelet-derived growth factor (PDGF) family, such as PDGF-AP, PDGF-BB and PDGF-AA; a member of the interleukin (IL) family, such as IL-1, IL-2, IL-3, IL-4, IL-5 or IL-6; or a member of the colony-stimulating factor (CSF) family, such as CSF-1, G-CSF, and GM-CSF. A growth factor may be a growth factor obtained from a tissue source, or can be a recombinant growth factor produced in vitro, in a cell culture, or in a microorganism using standard molecular biology techniques. In some aspects, a growth factor may be a bone morphogenetic protein, such as, in non-limiting example, BMP-1, BMP-2, BMP-3, BMP-4, BMP-5, BMP-6 or BMP-7. Any such growth factors may for example be

obtained by prior isolation from bone tissue including allogenic bone tissue. For example, one or more growth factors such as one or more BMPs may be isolated from allogenic bone and incorporated in the first carrier component, second carrier component, or cell composition.

[0097] The first carrier component, second carrier component, or cell composition as described herein may comprise, in addition to or instead of a growth factor, nutritional factors, hormones, peptides/proteins, or polysaccharides. Nutritional factors may include, but are not limited to, fatty acids, calcium, dextrose, glucose, glutamine, and vitamins such as vitamin A, B complex vitamins, vitamin C, vitamin D, vitamin E, or vitamin K. Hormones may include, but are not limited to, estrogen, testosterone, growth hormone, and thyroid hormone. Non-limiting examples of peptides or proteins include amino acids, link protein, GHK-copper peptide, BMP-13, BMP-14, PLAB, bone marrow aspirate lysate, and platelet lysate. Non-limiting examples of polysaccharides or monosaccharides includes carbohydrates, such as glucose or polymers thereof, dextran, hyaluronic acid (HyA), oligosaccharides of HyA, heparin, heparan sulfate, N-acetyl-glucosamine, and marine sulfated polysaccharides.

C. Injection Preparation Methods

i. 4-inlet Injection Preparation Methods

[0098] **Fig. 10** illustrates a method for preparing an injection using a four-inlet injection preparation device **100**. In an aspect, the present disclosure provides a method of preparing a multi-component injection, including obtaining a carrier syringe **104** including at least two barrels with a first carrier component in a first barrel and a second carrier component in a second barrel; coupling a first barrel of the carrier syringe **104** to the first inlet **111** of an injection preparation device **100**, and a second barrel of the carrier syringe **104** to the third inlet **113** of the injection preparation device **100**; coupling a cell delivery syringe **106** to the second inlet **112** of the injection preparation device **100**; and coupling a carrier delivery syringe **108** to the fourth inlet **114** of the injection preparation device **100**.

The method may further include transferring the first carrier component from the first barrel of the carrier syringe **104** to the cell delivery syringe **106** through the first conduit of the injection preparation device **100** and transferring the second carrier component from the second barrel of the carrier syringe **104** to the carrier delivery syringe **108** through the second conduit of the injection preparation device **100**. A dual plunger rod assembly **118** used with the carrier syringe **104** may be configured to transfer a predetermined amount of the first carrier component to the cell delivery syringe **106** and a predetermined amount of the second carrier component to the carrier delivery syringe **108**. The method may further include coupling a cell transfer syringe **204** to the injection preparation device **100**. In an aspect, the cell transfer syringe **204** may be coupled to the first inlet **111** of the injection preparation device **100**. The method may further include removing the carrier syringe **104** from the injection preparation device **100** and coupling a cell transfer syringe **204** containing a cell composition to the injection preparation device **100.** The first carrier component may be transferred from the cell delivery syringe **106** to the cell transfer syringe **204** though the first conduit, whereby the first carrier component is mixed with the cell composition to form a first cell/carrier mixture. The first cell/carrier mixture may then be transferred back to the cell delivery syringe **106** through the first conduit.

[0099] In another aspect, the present disclosure provides a method of preparing a multi-component injection, including filling a carrier syringe **104** including at least two barrels with a first carrier component in a first barrel and a second carrier component in a second barrel. The two barrels of the carrier syringe **104** may be coupled to the first and third inlets **111, 113** of an injection preparation device **100**, and the two barrels of the multi-barrel delivery syringe **116** may be coupled to the second and fourth inlets **112, 114** of the injection preparation device **100**. In an aspect, the method may include transferring the first carrier component from the first barrel of the carrier syringe **104** to a first barrel of the delivery syringe **116** through the first conduit of the injection preparation device, and transferring the second carrier component from the second barrel of the carrier syringe **104** to a second barrel of the delivery syringe **116** through the second conduit of the

injection preparation device **100**. A double-barrel plunger rod assembly **118** used with the carrier syringe **104** may be configured to transfer a predetermined amount of the first carrier component and a predetermined amount of the second carrier component to the delivery syringe **116**. The method may further include removing the carrier syringe **104** from the injection preparation device **100** and coupling a cell transfer syringe **204** containing a cell composition to the injection preparation device **100**. In an aspect, the method may include transferring the first carrier component from the first barrel of the delivery syringe **116** to the cell transfer syringe **204** though the first conduit, whereby the first carrier component is mixed with the cell composition to form a first cell/carrier mixture; and transferring the first cell/carrier mixture back to the first barrel of the delivery syringe **116** through the first conduit. The cell transfer syringe may be coupled to the first inlet of the of the injection preparation device. In an aspect, the method may further include decoupling the delivery syringe **116** from the injection preparation device **100**, where the first barrel of the delivery syringe **116** contains the first cell/carrier mixture and the second barrel of the delivery syringe **116** contains the second carrier component.

[0100] The method may further include coupling the delivery syringe **106, 108, 116** to a Y-connector **700** having a stem portion, and ejecting the first cell/carrier mixture from the first barrel of the delivery syringe **116** or the cell delivery syringe **106** and the second carrier component from the second barrel of the delivery syringe **116** or the carrier delivery syringe **108** through the Y-connector **700**, whereby the first cell/carrier mixture and the second carrier component are combined in the Y-connector stem portion to form a cell/carrier composition. The Y-connector **700** may be configured to reversibly couple to the cell delivery syringe **106** and to the carrier delivery syringe **108** or the multi-barrel delivery syringe **116**. The Y-connector **700** includes a connector body **702** having a first end and a second end, the first end defining at least two connector inlets for reversibly coupling the Y-connector **700** to the cell delivery syringe **106** and the carrier delivery syringe **108** or to the at least two barrels of the delivery syringe **116**. The method may further include coupling a dual lumen cannula **704** to the second

end of the Y-connector body **702** and coupling a spinal needle to the dual lumen cannula **704**.

[0101] In an aspect, the method may further include introducing a light source or light conduit, such as an optic fiber or endoscope, to expose photoactivated polymer(s) at or near the end of the dual lumen cannula. In one aspect, the light source and/or light conduit may run the length of the dual cannula. In various aspects, the light source and/or light conduit may be integral or attached to the Y-connector, dual cannula, spinal needle, or delivery syringe. During the repair of the spinal disc annulus it may be desired to use a light polymerizing polymer as a carrier for the delivery of biologic cells or drugs. The advantage in this arrangement is a single carrier component with the mixed in biologic cells or drugs may be sufficient instead of needing a two part carrier that reacts together. In an aspect, the carrier component may be polymerized by light which may be delivered via an integrated fiber optic in or on the spinal needle. This may allow for a rapid hardening of the photoactive polymer so it does not migrate and provide structural support similar to the current properties of the disc annulus. It also may allow for the contouring of the repair by controlled delivery and hardening of the polymer. In another aspect, using a light source with a photoactive polymer may allow for the construction of geometric structures to fit the deflect shape.

[0102] In one aspect, the method may include passing the spinal needle through a fiber optic endoscope. The endoscope may allow for illumination and viewing of the defects repair which may allow for the contouring (geometric construction) of the polymerized carrier component with mixed in biologic cells or drugs.

[0103] In another aspect, even if the carrier is multi-component and delivered via a multi-barrel delivery syringe, the polymerization rate of the delivered polymer may be ‘tuned’ via light intensity. In an aspect, the carrier component(s) may be exposed to light to initiate the reaction for polymer polymerization before the carrier component(s) enter the needle and thus would be reacting as it is progressing down the needle to be delivered. This may have the benefit of allowing for a lower profile (outer diameter) spinal needle for delivery.

[0104] The methods may further include injecting the cell/carrier composition into a tissue defect. In various aspects, the tissue may be, without limitation, bone, cartilage, tendon tissue, ligament tissue, soft tissue such as vascular tissue, dermal tissue or muscle tissue, neural tissue, or a combination thereof. In some other aspects, a site in need of tissue growth may include tendon tissue, ligament tissue, vascular tissue, dermal tissue, periodontal tissue, intervertebral disc tissue, hyaline cartilage, fibrous cartilage, elastic cartilage, a nerve tunnel or a combination thereof. In another aspect, the tissue may include but is not limited to bone, cartilage or soft tissue. In an aspect, the methods may further include injecting the cell/carrier composition into a degenerated intervertebral disc.

[0105] In various configurations, a site in need of tissue growth may include, without limitation, dermis, a rotator cuff tendon, an Achilles tendon, a ligament such as an anterior cruciate ligament (ACL), a posterior cruciate ligament, (PCL), a medial collateral ligament, a lateral collateral ligament or a periodontal figment, a sphincter such as an anal sphincter, a urethral sphincter, an esophageal sphincter or an antral sphincter, herniated tissue such as an abdominal hernia, a Cooper's hernia, a diaphragmatic hernia, an epigastric hernia, a femoral hernia, an incisional hernia, an inguinal hernia, an intervertebral disc hernia, a Littre's hernia, an obturator hernia, a pantaloon hernia, a perineal hernia, a properitoneal hernia, a Richter's hernia, a sciatic hernia, a sliding hernia, a Spigelian hernia or an umbilical hernia, an intervertebral disc nucleus, an intervertebral disc annulus, periosteal tissue, neural tissue such as central nervous system tissue (including spinal cord tissue) and demyelinated neural tissue, peripheral nervous system tissue, a nerve tunnel such as a nerve tunnel traversing bone tissue, a mitral valve, a tricuspid valve, an aortic heart valve, a pulmonary heart valve, vascular tissue comprising a stent, stenotic cardiovascular tissue, cartilage, costal cartilage, meniscus cartilage, epiglottic cartilage, laryngeal cartilage such as arytenoid cartilage, cricoid cartilage, cuneiform cartilage and corniculate cartilage, external ear cartilage, auditory tube cartilage, labral cartilage, articular cartilage, bone, bone defects/voids, muscle, and other soft tissues.

[0106] In an aspect, the method may further include monitoring the injection load using an injection load monitoring device **800** reversibly coupled to the cell delivery syringe **106** and the carrier delivery syringe **108** or the multi-barrel delivery syringe **116**. In an aspect, the injection load monitoring device **800** may include a mechanical load sensor **802** having an amplifier and an electrical coupling coupled thereto for coupling to a pressure display unit **808**; a syringe adapter **804** coupled to the mechanical load sensor **802** and a finger plate **806** coupled to the mechanical load sensor **802.** The syringe adapter **804** may have a first surface configured to engage an outward end portion of a plunger rod of a plunger rod assembly of the delivery syringe **116** or the cell delivery syringe **106** and the carrier delivery syringe **108**. In an aspect, the mechanical load sensor **802** may be selected from a miniature or subminiature load cell and a piezoresistive force sensor. The mechanical load sensor **802** may be operable for measuring a compression load of up to about 100 lb. In an aspect, the pressure display unit **808** may display a visual alarm, an auditory alarm, or both in response to the pressure applied to the delivery syringe **106, 108, 116**. The pressure display unit **800** may be directly coupled to the syringe adapter **804** or finger plate **806**. In an aspect, the pressure display unit **808** may be coupled to the mechanical load sensor wirelessly.

[0107] In another aspect, the method may include connecting a transfer shield **502** to a cell storage container **402** by penetrating a needle through the opening covered by a sterile seal. The transfer shield **502** may engage a syringe barrel, such as the cell delivery syringe. In an non-limiting example, the connector port may use a female luer port to reversibly engage a male luer-tipped syringe. The wall of the substantially tubular projection may define an opening therethrough so that the contents of the cell storage container may be visible when the shield is in use to penetrate the seal by contacting the seal with the hollow needle.

[0108] In an aspect, the prepared cell composition may include but is not limited to cells selected from neuronal stem cells, chondrocytes, notochordal cells, chondrogenic cells, mesenchymal stem cells, hematopoietic stem cells, and any pluripotent stem cells, including embryonic and induced pluripotent stem cells.

The prepared cell composition may include but is not limited to mesenchymal stem cells derived from at least one of bone marrow, adipose tissue, synovium, periosteum, post-partum connective tissue, placenta, cord blood, and umbilical cord. It should be understood that the methods encompass any method in which the cells selected for the cell/carrier composition match the tissue or tissues being repaired. Appropriate combinations of cells are also contemplated. For example, chondrogenic cells can be selected to repair cartilage tissue; osteogenic cells can be selected to repair bone; a combination of chondrogenic cells and osteogenic cells can be selected to repair damage to a combination of cartilage and bone; neural or neurogenic cells can be selected to repair cartilage nervous tissue.

[0109] In an aspect, the carrier syringe **104** may include two barrels and a double-barrel plunger rod assembly **118** configured to transfer a first predetermined amount of a first carrier component and a second predetermined amount of a second carrier component. The double-barrel plunger rod assembly **118** may include a first plunger rod for slidably engaging the first barrel of the carrier syringe and a second plunger rod for slidably engaging the second barrel of the carrier syringe, where the first plunger rod is shorter than the second plunger rod so that the first predetermined amount of the first carrier component is less than the second predetermined amount of the second carrier component.

[0110] In an aspect, the first carrier component may be thrombin and the second carrier component may be fibrinogen. Non-limiting examples of the first carrier component include thrombin, fibrinogen, poly(ethylene glycol) (PEG), poly(ethylene oxide) (PEO), poly(vinyl alcohol) (PVA), PEG–polystyrene copolymers (PEG)–(PST), polylactic acid (PLA), ethylene glycol–lactic acid copolymers, ethylene glycol–lactic acid–caprolactone copolymers, poly(d,l-lactide-*co*-ε-caprolactone), (poly)-anhydrides, anhydrides, urethanes, polysaccharides, dextran, collagen, hyaluronic acid, diethyl fumarate/poly(propylene fumarate), chitosan, a caprolactone polymer such as polycaprolactone (PCL), polyglycolic acid (PGA), or a copolymer of polylactic acid and polyglycolic acid (PLGA), and combinations thereof. In another aspect, the first carrier component may be a photoactive polymerizing polymer. Non-limiting

examples of photoactive polymerizing polymers or monomers include collagen, styrene, N-Vinylpyrrolidone, acrylates, epoxides, urethanes, polyethers, and polyesters. In an aspect, the first carrier component may further include a photoinitiator. In another aspect, the second carrier component may include a photoinitiator. Non-limiting examples of photoinitiators include Diazopyruvate, Rose Bengal, riboflavin, riboflavin 5-monophosphate sodium salt dehydrate, m-tetrahydroxyphenylchlorin (mTHPC), benzophenone, xanthones, quinones, benzoin ethers, acetophenones, benzoyl oximes, and acylphosphines.

[0111] It should be understood therefore that the carrier, such as a protein carrier, used to deliver cells to target tissues in need of repair may be selected from a variety of natural and/or engineered proteins, the most commonly encountered being collagen. Additionally, in the presence of a suitable non-toxic photoactive agent, a light source can be applied to crosslink the carrier material containing a cell suspension, thereby fixing the cells within the construct and further anchoring the delivered structural matrix to exposed collagen fibrils within adjacent native tissue. Note that either continuous or pulsed delivery of the irradiation source may be utilized to enhance crosslinking as well as depth of desired cross-linking. Common such photoinitiators include but are not limited to: Diazopyruvate - 330-400 nm light source; 0.1-0.5 mM riboflavin - 475-480 nm xenon light 10-40s; and m-tetrahydroxyphenylchlorin (mTHPC; 0.03 mg/mL in liposomes) - 652 nm light @ 10-20 j/cm2.

[0112] Thus, in any of the devices, kits and methods described herein, a non-limiting example use of a photoactive polymerizing polymer is as follows: a first carrier component and a second component can be prepared in any way which, when the two carrier components are combined, combines a photoactive polymerizing polymer and a photinitiator. Alternatively, the first carrier component can include both a photoactive polymerizing polymer and a photinitiator, and the second carrier component can include other materials as detailed elsewhere herein. For example the photoactive polymerizing polymer can be high density collagen (HDC) and the photoinitiator can be riboflavin. Once combined, the photoactive polymerizing polymer and photinitiator are then exposed to an

appropriate wavelength of light given the selected photinitiator. For example, if HDC and riboflavin are used, once combined the HDC is photochemically cross-linked by exposure to an appropriate wavelength of light for riboflavin, for example about 458 nm. The resulting photochemical cross-linking of the HDC provides a gel scaffold that promotes cell viability and reduces gel contraction. (*See, e.g.*, S. Ibusuki et al., *Photochemically Cross-Linked Collagen Gels as Three-Dimensional Scaffolds for Tissue Engineering,* TISSUE ENGINEERING 13(8): 1995-2001 (2007).

[0113] In various aspects, the first predetermined amount may be from about 0.5 cc to about 1.5 cc, from about 0.5 to about 0.7 cc, from about 0.6 cc to about 0.8 cc, from about 0.7 cc to about 0.9 cc, from about 0.8 cc to about 1.0 cc, from about 0.9 cc to about 1.1 cc, from about 1.0 cc to about 1.2 cc, from about 1.1 cc to about 1.3 cc, from about 1.2 cc to about 1.4 cc, and from about 1.3 cc to about 1.5 cc. The second predetermined amount may be from about 0.5 cc to about 1.5 cc, from about 0.5 to about 0.7 cc, from about 0.6 cc to about 0.8 cc, from about 0.7 cc to about 0.9 cc, from about 0.8 cc to about 1.0 cc, from about 0.9 cc to about 1.1 cc, from about 1.0 cc to about 1.2 cc, from about 1.1 cc to about 1.3 cc, from about 1.2 cc to about 1.4 cc, and from about 1.3 cc to about 1.5 cc. In one aspect, the first predetermined amount may be about 0.6 cc and the second predetermined amount may be about 1.1 cc.

[0114] In any of the devices, kits and methods described herein, the first carrier component, second carrier component, or cell composition may optionally include one or more growth factors, osteostimulative agents, and/or bone morphogenetic proteins, which may be obtained by prior isolation from allogenic bone. Non-limiting examples of such growth factors that may be included into a first or second carrier component or cell composition of the present teachings include a member of the TGF-β superfamily, such as TGF-β1, TGF-β2, TGF-β3, or a bone morphogenetic protein (BMP); a growth differentiation factor; ADMP-1; a fibroblast growth factor (FGF) such as acidic FGF or basic FGF; a member of the hedgehog family of proteins, such as indian hedgehog, sonic hedgehog, or desert hedgehog; a platelet-derived growth factor, an interleukin; a colony-stimulating

factor; an activin; a member of the insulin-like growth factor (IGF) family, such as IGF-I or IGF-II; a member of the platelet-derived growth factor (PDGF) family, such as PDGF-AP, PDGF-BB and PDGF-AA; a member of the interleukin (IL) family, such as IL-1, IL-2, IL-3, IL-4, IL-5 or IL-6; or a member of the colony-stimulating factor (CSF) family, such as CSF-1, G-CSF, and GM-CSF. A growth factor may be a growth factor obtained from a tissue source, or can be a recombinant growth factor produced in vitro, in a cell culture, or in a microorganism using standard molecular biology techniques. In some aspects, a growth factor may be a bone morphogenetic protein, such as, in non-limiting example, BMP-1, BMP-2, BMP-3, BMP-4, BMP-5, BMP-6 or BMP-7. Any such growth factors may for example be obtained by prior isolation from bone tissue including allogenic bone tissue. For example, one or more growth factors such as one or more BMPs may be isolated from allogenic bone and incorporated in the first carrier component, second carrier component, or cell composition.

[0115] The first carrier component, second carrier component, or cell composition as described herein may comprise, in addition to or instead of a growth factor, nutritional factors, hormones, peptides/proteins, or polysaccharides. Nutritional factors may include, but are not limited to, fatty acids, calcium, dextrose, glucose, glutamine, and vitamins such as vitamin A, B complex vitamins, vitamin C, vitamin D, vitamin E, or vitamin K. Hormones may include, but are not limited to, estrogen, testosterone, growth hormone, and thyroid hormone. Non-limiting examples of peptides or proteins include amino acids, link protein, GHK-copper peptide, BMP-13, BMP-14, PLAB, bone marrow aspirate lysate, and platelet lysate. Non-limiting examples of polysaccharides or monosaccharides includes carbohydrates, such as glucose or polymers thereof, dextran, hyaluronic acid (HyA), oligosaccharides of HyA, heparin, heparan sulfate, N-acetyl-glucosamine, and marine sulfated polysaccharides.

ii. 5-inlet Injection Preparation Methods

[0116] **Fig. 11** illustrates a method for preparing an injection using a five-inlet injection preparation device **200**. In an aspect, the present disclosure

provides a method of preparing a multi-component injection, including obtaining a carrier syringe **104** including at least two barrels with a first carrier component in a first barrel and a second carrier component in a second barrel; coupling a first barrel of the carrier syringe **104** to the first inlet **211** of the injection preparation device **200**, and a second barrel of the carrier syringe **104** to the third inlet **213** of the injection preparation device **200**; coupling a cell delivery syringe **106** to the second inlet **212** of the injection preparation device **200**; coupling a cell transfer syringe **204** to the fifth inlet **215** of the injection preparation device **200**; and coupling a carrier delivery syringe **108** to the fourth inlet **214** of the injection preparation device **200**. The method may further include transferring the second carrier component from the second barrel of the carrier syringe **104** to the carrier delivery syringe **108** through the second conduit of the injection preparation device. In an aspect, the flow path may be limited through the first conduit of the injection preparation device **200** to between the first inlet **211** and the fifth inlet **215.** The method may also include transferring the first carrier component from the first barrel of the carrier syringe **104** to the cell transfer syringe **204** through the first conduit of the injection preparation device **200**. A double-barrel plunger rod assembly **118** used with the carrier syringe **104** is configured to transfer a predetermined amount of the first carrier component to the cell transfer syringe **204** and a predetermined amount of the second carrier component to the carrier delivery syringe **108**, whereby the first carrier component mixes with the contents of the cell transfer syringe **204**. The method may further include limiting the flow path through the first conduit **211** of the injection preparation device **200** to between the fifth inlet **215** and the second inlet **212** and transferring the mixture in the cell transfer syringe **204** to the cell delivery syringe **106**. The method may further include decoupling the cell delivery syringe **106** and the carrier delivery syringe **108** from the injection preparation device, where the carrier delivery syringe **108** contains the first second carrier component and the cell delivery syringe **106** contains a first cell/carrier mixture.

[0117] In another aspect, the present disclosure provides a method of preparing a multi-component injection, including filling a carrier syringe **104**

including at least two barrels with a first carrier component in a first barrel and a second carrier component in a second barrel; coupling the two barrels of the carrier syringe **104** to the first and third inlets **211, 213** of an injection preparation device **200**, and coupling the two barrels of the multi-barrel delivery syringe **116** to the second and fourth inlets **212, 214** of the injection preparation device **200**, and transferring the first carrier component from the first barrel of the carrier syringe **104** to a first barrel of the delivery syringe **116** through the first conduit of the injection preparation device **200**, and the second carrier component from the second barrel of the carrier syringe **104** to a second barrel of the delivery syringe **116** through the second conduit of the injection preparation device **200**, where a double-barrel plunger rod assembly **118** used with the carrier syringe **104** may be configured to transfer a predetermined amount of the first carrier component and a predetermined amount of the second carrier component to the delivery syringe **116**. The method may further include removing the carrier syringe **104** from the injection preparation device **200**; coupling a cell transfer syringe **204** to the injection preparation device **200**, where the cell transfer syringe **204** contains a cell composition; transferring the first carrier component from the first barrel of the delivery syringe **116** to the cell transfer syringe **204** though the first conduit, whereby the first carrier component is mixed with the cell composition to form a first cell/carrier mixture; and transferring the first cell/carrier mixture back to the first barrel of the delivery syringe **116** through the first conduit. The method may further include decoupling the delivery syringe **116** from the injection preparation device, where the first barrel of the delivery syringe **116** contains the first cell/carrier mixture and the second barrel of the delivery syringe **116** contains the second carrier component.

[0118] The method may further include coupling the delivery syringe **106, 108, 116** to a Y-connector **700** having a stem portion, and ejecting the first cell/carrier mixture from the first barrel of the delivery syringe **116** or the cell delivery syringe **106** and the second carrier component from the second barrel of the delivery syringe **116** or the carrier delivery syringe **108** through the Y-connector **700**, whereby the first cell/carrier mixture and the second carrier

component are combined in the Y-connector stem portion to form a cell/carrier composition. The Y-connector **700** may be configured to reversibly couple to the cell delivery syringe **106** and to the carrier delivery syringe **108** or the multi-barrel delivery syringe **116**, and the Y-connector **700** includes a connector body **702** having a first end and a second end, the first end defining at least two connector inlets for reversibly coupling the Y-connector **700** to the cell delivery syringe **106** and the carrier delivery syringe **108** or to the at least two barrels of the delivery syringe **116**; the method further including coupling a dual lumen cannula **704** to the second end of the Y-connector body **702**, and coupling a spinal needle to the dual lumen cannula **704**.

[0119] In an aspect, the method may further include introducing a light source or light conduit, such as an optic fiber or endoscope, to expose photoactivated polymer(s) at or near the end of the dual lumen cannula. In one aspect, the light source and/or light conduit may run the length of the dual cannula. In various aspects, the light source and/or light conduit may be integral or attached to the Y-connector, dual cannula, spinal needle, or delivery syringe. During the repair of the spinal disc annulus it may be desired to use a light polymerizing polymer as a carrier for the delivery of biologic cells or drugs. The advantage in this arrangement is a single carrier component with the mixed in biologic cells or drugs may be sufficient instead of needing a two part carrier that reacts together. In an aspect, the carrier component may be polymerized by light which may be delivered via an integrated fiber optic in or on the spinal needle. This may allow for a rapid hardening of the photoactive polymer so it does not migrate and provide structural support similar to the current properties of the disc annulus. It also may allow for the contouring of the repair by controlled delivery and hardening of the polymer. In another aspect, using a light source with a photoactive polymer may allow for the construction of geometric structures to fit the deflect shape.

[0120] In one aspect, the method may include passing the spinal needle through a fiber optic endoscope. The endoscope may allow for illumination and viewing of the defects repair which may allow for the contouring (geometric

construction) of the polymerized carrier component with mixed in biologic cells or drugs.

[0121] In another aspect, even if the carrier is multi-component and delivered via a multi-barrel delivery syringe, the polymerization rate of the delivered polymer may be 'tuned' via light intensity. In an aspect, the carrier component(s) may be exposed to light to initiate the reaction for polymer polymerization before the carrier component(s) enter the needle and thus would be reacting as it is progressing down the needle to be delivered. This may have the benefit of allowing for a lower profile (outer diameter) spinal needle for delivery.

[0122] The methods may further include injecting the cell/carrier composition into a tissue defect. In various aspects, a tissue may be, without limitation, bone, cartilage, tendon tissue, ligament tissue, soft tissue such as vascular tissue, dermal tissue or muscle tissue, neural tissue, or a combination thereof. In some other aspects, a site in need of tissue growth may include tendon tissue, ligament tissue, vascular tissue, dermal tissue, periodontal tissue, intervertebral disc tissue, hyaline cartilage, fibrous cartilage, elastic cartilage, a nerve tunnel or a combination thereof. In another aspect, the tissue may include but is not limited to bone, cartilage or soft tissue. In an aspect, the methods may further include injecting the cell/carrier composition into a degenerated intervertebral disc.

[0123] In various configurations, a site in need of tissue growth may include, without limitation, dermis, a rotator cuff tendon, an Achilles tendon, a ligament such as an anterior cruciate ligament (ACL), a posterior cruciate ligament, (PCL), a medial collateral ligament, a lateral collateral ligament or a periodontal figment, a sphincter such as an anal sphincter, a urethral sphincter, an esophageal sphincter or an antral sphincter, herniated tissue such as an abdominal hernia, a Cooper's hernia, a diaphragmatic hernia, an epigastric hernia, a femoral hernia, an incisional hernia, an inguinal hernia, an intervertebral disc hernia, a Littre's hernia, an obturator hernia, a pantaloon hernia, a perineal hernia, a properitoneal hernia, a Richter's hernia, a sciatic hernia, a sliding hernia, a Spigelian hernia or an umbilical hernia, an intervertebral disc nucleus, an intervertebral disc annulus,

periosteal tissue, neural tissue such as central nervous system tissue (including spinal cord tissue) and demyelinated neural tissue, peripheral nervous system tissue, a nerve tunnel such as a nerve tunnel traversing bone tissue, a mitral valve, a tricuspid valve, an aortic heart valve, a pulmonary heart valve, vascular tissue comprising a stent, stenotic cardiovascular tissue, cartilage, costal cartilage, meniscus cartilage, epiglottic cartilage, laryngeal cartilage such as arytenoid cartilage, cricoid cartilage, cuneiform cartilage and corniculate cartilage, external ear cartilage, auditory tube cartilage, labral cartilage, articular cartilage, bone, bone defects/voids, muscle, and other soft tissues.

[0124] In an aspect, the method may further include monitoring the injection load using an injection load monitoring device **800** reversibly coupled to the cell delivery syringe **106** and the carrier delivery syringe **108** or the multi-barrel delivery syringe **116**, the injection load monitoring device **800** may include a mechanical load sensor **802** having an amplifier and an electrical coupling coupled thereto for coupling to a pressure display unit **808**; a syringe adapter **804** coupled to the mechanical load sensor **802**, the syringe adapter **804** having a first surface configured to engage an outward end portion of a plunger rod of a plunger rod assembly of the delivery syringe **116** or the cell delivery syringe **106** and the carrier delivery syringe **108**; and a finger plate **806** coupled to the mechanical load sensor **802**.

[0125] In an aspect, the mechanical load sensor **802** may be selected from a miniature or subminiature load cell and a piezoresistive force sensor. The mechanical load sensor **802** may be operable for measuring a compression load of up to about 100 lb. In an aspect, the pressure display unit **808** may display a visual alarm, an auditory alarm, or both in response to the pressure applied to the delivery syringe **106, 108, 116**. The pressure display unit **800** may be directly coupled to the syringe adapter **804** or finger plate **806**. In an aspect, the pressure display unit **808** may be coupled to the mechanical load sensor wirelessly.

[0126] In another aspect, the method may include connecting a transfer shield **502** to a cell storage container **402** by penetrating a needle through the opening covered by a sterile seal. The transfer shield **502** may engage a syringe

barrel, such as the cell delivery syringe. In an non-limiting example, the connector port may use a female luer port to reversibly engage a male luer-tipped syringe. The wall of the substantially tubular projection may define an opening therethrough so that the contents of the cell storage container may be visible when the shield is in use to penetrate the seal by contacting the seal with the hollow needle.

[0127] In an aspect, the prepared cell composition may include but is not limited to cells selected from adipocytes, neuronal stem cells, chondrocytes, notochordal cells, chondrogenic cells, mesenchymal stem cells, hematopoietic stem cells, and any pluripotent stem cells including embryonic and induced pluripotent stem cells. The prepared cell composition may include but is not limited to mesenchymal stem cells derived from at least one of bone marrow, adipose tissue, synovium, periosteum, post-partum connective tissue, placenta, cord blood, and umbilical cord.

[0128] In various aspects, without limitation, the neuronal stem cells may be used to repair neural tissue, the chrondrocytes or chondrogenic cells may be used to repair cartilage, the notochordal cells may be used to repair intervertebral disc tissue, and the mesenchymal stem cells may be used to repair bone, cartilage, or intervertebral disc tissue.

[0129] In an aspect, the carrier syringe **104** may include two barrels and a double-barrel plunger rod assembly **118** configured to transfer a first predetermined amount of a first carrier component and a second predetermined amount of a second carrier component. The double-barrel plunger rod assembly **118** may include a first plunger rod for slidably engaging the first barrel of the carrier syringe and a second plunger rod for slidably engaging the second barrel of the carrier syringe, where the first plunger rod is shorter than the second plunger rod so that the first predetermined amount of the first carrier component is less than the second predetermined amount of the second carrier component.

[0130] In an aspect, the first carrier component may be thrombin and the second carrier component may be fibrinogen. Non-limiting examples of the first carrier component include thrombin, fibrinogen, poly(ethylene glycol) (PEG), poly(ethylene oxide) (PEO), poly(vinyl alcohol) (PVA), PEG–polystyrene

copolymers (PEG)–(PST), poly(lactic acid), ethylene glycol–lactic acid copolymers, ethylene glycol–lactic acid–caprolactone copolymers, poly(d,l-lactide-*co*-ε-caprolactone), (poly)-anhydrides, anhydrides, urethanes, polysaccharides, dextran, collagen, hyaluronic acid, diethyl fumarate/poly(propylene fumarate), chitosan, a caprolactone polymer such as polycaprolactone (PCL), polyglycolic acid (PGA), or a copolymer of polylactic acid and polyglycolic acid (PLGA), and combinations thereof. In another aspect, the first carrier component may be a photoactive polymerizing polymer. Non-limiting examples of photoactive polymerizing polymers or monomers include collagen, styrene, N-Vinylpyrrolidone, acrylates, epoxides, urethanes, polyethers, and polyesters. In an aspect, the first carrier component may further include a photoinitiator. In another aspect, the second carrier component may include a photoinitiator. Non-limiting examples of photoinitiators include Diazopyruvate, Rose Bengal, riboflavin, riboflavin 5-monophosphate sodium salt dehydrate, m-tetrahydroxyphenylchlorin (mTHPC), benzophenone, xanthones, quinones, benzoin ethers, acetophenones, benzoyl oximes, and acylphosphines.

[0131] In various aspects, the first predetermined amount may be from about 0.5 cc to about 1.5 cc, from about 0.5 to about 0.7 cc, from about 0.6 cc to about 0.8 cc, from about 0.7 cc to about 0.9 cc, from about 0.8 cc to about 1.0 cc, from about 0.9 cc to about 1.1 cc, from about 1.0 cc to about 1.2 cc, from about 1.1 cc to about 1.3 cc, from about 1.2 cc to about 1.4 cc, and from about 1.3 cc to about 1.5 cc. The second predetermined amount may be from about 0.5 cc to about 1.5 cc, from about 0.5 to about 0.7 cc, from about 0.6 cc to about 0.8 cc, from about 0.7 cc to about 0.9 cc, from about 0.8 cc to about 1.0 cc, from about 0.9 cc to about 1.1 cc, from about 1.0 cc to about 1.2 cc, from about 1.1 cc to about 1.3 cc, from about 1.2 cc to about 1.4 cc, and from about 1.3 cc to about 1.5 cc. In one aspect, the first predetermined amount may be about 0.6 cc and the second predetermined amount may be about 1.1 cc.

[0132] In any of the devices, kits and methods described herein, the first carrier component, second carrier component, or cell composition may optionally include one or more growth factors, osteostimulative agents, and/or bone

morphogenetic proteins, which may be obtained by prior isolation from allogenic bone. Non-limiting examples of such growth factors that may be included into a first or second carrier component or cell composition of the present teachings include a member of the TGF-β superfamily, such as TGF-β1, TGF-β2, TGF-β3, or a bone morphogenetic protein (BMP); a growth differentiation factor; ADMP-1; a fibroblast growth factor (FGF) such as acidic FGF or basic FGF; a member of the hedgehog family of proteins, such as indian hedgehog, sonic hedgehog, or desert hedgehog; a platelet-derived growth factor, an interleukin; a colony-stimulating factor; an activin; a member of the insulin-like growth factor (IGF) family, such as IGF-I or IGF-II; a member of the platelet-derived growth factor (PDGF) family, such as PDGF-AP, PDGF-BB and PDGF-AA; a member of the interleukin (IL) family, such as IL-1, IL-2, IL-3, IL-4, IL-5 or IL-6; or a member of the colony-stimulating factor (CSF) family, such as CSF-1, G-CSF, and GM-CSF. A growth factor may be a growth factor obtained from a tissue source, or can be a recombinant growth factor produced in vitro, in a cell culture, or in a microorganism using standard molecular biology techniques. In some aspects, a growth factor may be a bone morphogenetic protein, such as, in non-limiting example, BMP-1, BMP-2, BMP-3, BMP-4, BMP-5, BMP-6 or BMP-7. Any such growth factors may for example be obtained by prior isolation from bone tissue including allogenic bone tissue. For example, one or more growth factors such as one or more BMPs may be isolated from allogenic bone and incorporated in the first carrier component, second carrier component, or cell composition.

[0133] The first carrier component, second carrier component, or cell composition as described herein may comprise, in addition to or instead of a growth factor, nutritional factors, hormones, peptides/proteins, or polysaccharides. Nutritional factors may include, but are not limited to, fatty acids, calcium, dextrose, glucose, glutamine, and vitamins such as vitamin A, B complex vitamins, vitamin C, vitamin D, vitamin E, or vitamin K. Hormones may include, but are not limited to, estrogen, testosterone, growth hormone, and thyroid hormone. Non-limiting examples of peptides or proteins include amino acids, link protein, GHK-copper peptide, BMP-13, BMP-14, PLAB, bone marrow aspirate lysate, and platelet

lysate. Non-limiting examples of polysaccharides or monosaccharides includes carbohydrates, such as glucose or polymers thereof, dextran, hyaluronic acid (HyA), oligosaccharides of HyA, heparin, heparan sulfate, N-acetyl-glucosamine, and marine sulfated polysaccharides.

Example 1: Photo-cross-linked Carrier

[0134] To demonstrate the use of a photoactive polymerizing polymer, the following example was performed. Acid soluble Type 1 collagen (pH 1.0) sourced from bovine skin or tendon (1-40 mg/mL) was used to prepare hydrogel carrier for cell delivery. A collagen solution was neutralized to pH 7.4 using 2.2% sodium bicarbonate/0.8M sodium hydroxide. A photo-initiator (riboflavin5-mono-phosphate sodium salt [Sigma-Aldrich]) was added to the collagen solution to yield a final concentration of 0.5 mM. A chondrocyte suspension (1 million per mL human juvenile articular chondrocytes) was then mixed 1:1 with the collagen solution containing 0.5mM riboflavin, pipetted at increasing volume into 96 well plates (50-400 microliters) and exposed to blue light for 40 seconds. Plates were then incubated at 37C for 24 and 48 hrs, at which time the metabolic activity was assessed using PrestoBlue, according to manufacturer's instructions (Life Technologies). Two additional plates were set up in the absence of hydrogel to demonstrate that photo-crosslinking has a negligible effect on chondrocyte viability and measured metabolic activity 24 and 48 hrs post-plating.

[0135] All patents and publications mentioned in the specification are indicative of the levels of those skilled in the art to which the present disclosure pertains. All patents and publications are herein incorporated by reference to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference.

CLAIMS

What is claimed is:

1. An injection preparation device comprising:
    a body adapted to reversibly couple to a multi-barrel carrier syringe and a multi-barrel delivery syringe, the body comprising:
        a first transfer portion defining a first inlet configured to reversibly couple to a first barrel of the multi-barrel carrier syringe and a second inlet configured to reversibly couple to a first barrel of the multi-barrel delivery syringe, wherein the first inlet and second inlet communicate through a first conduit through the body; and
        a second transfer portion defining a third inlet configured to reversibly couple to a second barrel of the multi-barrel carrier syringe and a fourth inlet configured to reversibly couple to a second barrel of the multi-barrel delivery syringe, wherein the third and fourth inlets communicate through a second conduit through the body; and
    an injection load monitoring device configured to reversibly couple to a delivery syringe.
2. The injection preparation device of claim 1, wherein the injection load monitoring device comprises:
    a mechanical load sensor having an amplifier and an electrical coupling coupled thereto for coupling to a pressure display unit;
    a syringe adapter coupled to the mechanical load sensor, the syringe adapter having a first surface configured to engage an outward end portion of a plunger rod of a plunger rod assembly of the delivery syringe; and
    a finger plate coupled to the mechanical load sensor.

3. The injection preparation device of claim 2, wherein the mechanical load sensor is selected from the group consisting of a miniature or subminiature load cell and a piezoresistive mechanical load sensor.

4. The injection preparation device of claim 2, wherein the mechanical load sensor is operable for measuring a compression load of up to about 100 lb.

5. The injection preparation device of claim 2, wherein the mechanical load display unit displays a visual alarm, an auditory alarm, or both in response to the mechanical load applied to the delivery syringe.

6. The injection preparation device of claim 2, wherein the mechanical load display unit is directly coupled to the syringe adapter or finger plate.

7. The injection preparation device of claim 2, wherein the pressure display unit is configured for wireless communication with the mechanical load sensor.

8. The injection preparation device of claim 1, wherein the body is further configured to reversibly couple to a cell transfer syringe.

9. An injection preparation kit comprising the injection preparation device of claim 8, and at least one of the multi-barrel carrier syringe, the multi-barrel delivery syringe and the cell transfer syringe.

10. The injection preparation kit of claim 9, comprising the multi-barrel carrier syringe, wherein the carrier syringe comprises two barrels and a double-barrel plunger rod assembly configured to transfer a first predetermined amount of a first carrier component and a second predetermined amount of a second carrier component.

11. The injection preparation kit of claim 10, wherein the double-barrel plunger rod assembly comprises a first plunger rod for slidably engaging the first barrel of the carrier syringe and a second plunger rod for slidably engaging the second barrel of the carrier syringe, wherein the first plunger rod is

shorter than the second plunger rod so that the first predetermined amount of the first carrier component is less than the second predetermined amount of the second carrier component.

12. The injection preparation kit of claim 11, wherein the first carrier component is thrombin and the second carrier component is fibrinogen.

13. The injection preparation kit of claim 12, wherein the first predetermined amount is about 0.5 to about 0.7 cc and the second predetermined amount is about 1.0 to about 1.2 cc.

14. The injection preparation kit of claim 9, comprising the multi-barrel delivery syringe, wherein delivery syringe comprises two barrels and a double-barrel plunger rod assembly.

15. An injection preparation device comprising:
a body configured to reversibly engage a multi-barrel carrier syringe, a cell transfer syringe, a cell delivery syringe and a carrier delivery syringe, the body comprising:
a first transfer portion defining a first inlet configured to reversibly couple to a first barrel of the multi-barrel carrier syringe, a second inlet configured to reversibly couple to the barrel of the cell delivery syringe, and a fifth inlet configured to reversibly couple to the barrel of the cell transfer syringe, wherein the first, second, and fifth inlets communicate through a first conduit through the body; and
a second transfer portion defining a third inlet configured to reversibly couple to a second barrel of the multi-barrel carrier syringe, a fourth inlet configured to reversibly couple to the barrel of the carrier delivery syringe, wherein the third and fourth inlets communicate through a second conduit through the body; and
an injection load monitoring device configured to reversibly couple to a

delivery syringe.

16. The injection preparation device of claim 15, wherein the injection load monitoring device comprises:

a mechanical load sensor having an amplifier and an electrical coupling coupled thereto for coupling to a pressure display unit;

a syringe adapter coupled to the mechanical load sensor, the syringe adapter having a first surface configured to engage an outward end portion of a plunger rod of a plunger rod assembly of the delivery syringe; and

a finger plate coupled to the mechanical load sensor.

17. The injection preparation device of claim 16, wherein the mechanical load sensor is selected from the group consisting of a miniature or subminiature load cell and a piezoresistive mechanical load sensor.

18. The injection preparation device of claim 16, wherein the mechanical load sensor is operable for measuring a compression load of up to about 100 lb.

19. The injection preparation device of claim 16, wherein the mechanical load display unit displays a visual alarm, an auditory alarm, or both in response to the mechanical load applied to the delivery syringe.

20. The injection preparation device of claim 16, wherein the mechanical load display unit is directly coupled to the syringe adapter or finger plate.

21. The injection preparation device of claim 16, wherein the pressure display unit is configured for wireless communication with the mechanical load sensor.

22. The injection preparation device of claim 15, wherein the first transfer portion comprises a two-way valve configured to limit a fluid path to one of: i) between the first and second inlets, and ii) between the first and fifth inlets.

23. The injection preparation device of claim 15, wherein the third inlet defined by the second transfer portion comprises a one-way valve.

24. An injection preparation kit comprising the injection preparation device of claim 15, and at least one of a multi-barrel carrier syringe, a cell transfer syringe, a cell delivery syringe and a carrier delivery syringe.

25. The injection preparation kit of claim 24, comprising the multi-barrel carrier syringe, wherein the carrier syringe comprises two barrels and a double-barrel plunger rod assembly configured to transfer a first predetermined amount of a first carrier component and a second predetermined amount of a second carrier component.

26. The injection preparation kit of claim 25, wherein the double-barrel plunger rod assembly comprises a first plunger rod for slidably engaging the first barrel of the carrier syringe and a second plunger rod for slidably engaging the second barrel of the carrier syringe, wherein the first plunger rod is shorter than the second plunger rod so that the first predetermined amount of the first carrier component is less than the second predetermined amount of the second carrier component.

27. The injection preparation kit of claim 26, wherein the first carrier component is thrombin and the second carrier component is fibrinogen.

28. The injection preparation kit of claim 27, wherein the first predetermined amount is about 0.5 to about 0.7 cc and the second predetermined amount is about 1.0 to about 1.2 cc.

29. A transfer shield for use with a cell storage container having an opening covered by a sterile seal capable of penetration by a hollow needle, the transfer shield comprising:

a body having a first surface and a second surface and defining an opening therethrough from the first surface to the second surface, the opening having a rim;

a substantially tubular projection from the first surface defining a wall surrounding the opening;

the hollow needle disposed perpendicular to the first surface from within the wall, wherein the hollow needle is coupled to the rim of the opening and the hollow needle has a length less than or equal to a depth of the tubular projection from the first surface.

30. The transfer shield of claim 29, further comprising a connector port projecting from the body second surface, wherein the connector port defines a wall surrounding the opening and wherein the connector port is configured to engage a syringe barrel.

31. An injection preparation kit for transferring a prepared cell composition from a cell storage container to a cell transfer syringe, the kit comprising the injection preparation device of claim 1 and the transfer shield of claim 29.

32. An injection preparation kit for transferring a prepared cell composition from a cell storage container to a cell transfer syringe, the kit comprising the injection preparation device of claim 15 and the transfer shield of claim 29.

33. The injection preparation kit of claim 9, further comprising a cell storage container comprising: a substantially cylindrical body defining a central lumen, a first end and a second end, wherein the first end defines a fill opening, and the second end defines an access port, and a flexible sealing element over the access port; and a cap configured to seal the fill opening, wherein the fill opening and access port communicate with the central lumen.

34. The injection preparation kit of claim 33, wherein the cell storage container contains a prepared cell composition for transfer to a delivery syringe.

35. The injection preparation kit of claim 33, wherein the second end further defines a connector port for reversibly engaging a connector port of a second device.

36. The injection preparation kit of claim 9, further comprising an amount of the prepared cell composition, wherein the prepared cell composition comprises cells selected from the group consisting of: neuronal stem cells; chondrocytes, notochordal cells, chondrogenic cells, mesenchymal stem cells, hematopoietic stem cells, pluripotent stem cells, and induced pluripotent stem cells.

37. The injection preparation kit of claim 9, further comprising an amount of at least a first carrier component.

38. The injection preparation kit of claim 37, wherein the first carrier component is a photoactive polymerizing polymer.

39. The injection preparation kit of claim 37, wherein the first carrier component comprises polymers selected from the group consisting of: poly(ethylene glycol) (PEG), poly(ethylene oxide) (PEO), poly(vinyl alcohol) (PVA), PEG–polystyrene copolymers (PEG)–(PST), poly(lactic acid), ethylene glycol–lactic acid copolymers, ethylene glycol–lactic acid–caprolactone copolymers, poly(d,l-lactide-*co*-ε-caprolactone), (poly)-anhydrides, anhydrides, urethanes, polysaccharides, dextran, collagen, hyaluronic acid, diethyl fumarate/poly(propylene fumarate), chitosan, and combinations thereof.

40. The injection preparation kit of claim 37, further comprising an amount of a second carrier component, wherein the amounts of the first and the second carrier components are packaged separately.

41. The injection preparation kit of claim 40, wherein the first carrier component is thrombin and the second carrier component is fibrinogen.

42. The injection preparation kit of claim 24, further comprising a cell storage container comprising: a substantially cylindrical body defining a central lumen, a first end and a second end, wherein the first end defines a fill opening, and the second end defines an access port, and a flexible sealing

element over the access port; and a cap configured to seal the fill opening, wherein the fill opening and access port communicate with the central lumen.

43. The injection preparation kit of claim 42, wherein the cell storage container contains a prepared cell composition for transfer to a delivery syringe.

44. The injection preparation kit of claim 42, wherein the second end further defines a connector port for reversibly engaging a connector port of a second device.

45. The injection preparation kit of claim 24, further comprising an amount of the prepared cell composition, wherein the prepared cell composition comprises cells selected from the group consisting of: neuronal stem cells; chondrocytes, notochordal cells, chondrogenic cells, mesenchymal stem cells, hematopoietic stem cells, pluripotent stem cells, and induced pluripotent stem cells.

46. The injection preparation kit of claim 24, further comprising an amount of at least a first carrier component.

47. The injection preparation kit of claim 46, wherein the first carrier component is a photoactive polymerizing polymer.

48. The injection preparation kit of claim 46, wherein the first carrier component comprises polymers selected from the group consisting of: poly(ethylene glycol) (PEG), poly(ethylene oxide) (PEO), poly(vinyl alcohol) (PVA), PEG–polystyrene copolymers (PEG)–(PST), poly(lactic acid), ethylene glycol–lactic acid copolymers, ethylene glycol–lactic acid–caprolactone copolymers, poly(d,l-lactide-*co*-ε-caprolactone), (poly)-anhydrides, anhydrides, urethanes, polysaccharides, dextran, collagen, hyaluronic acid, diethyl fumarate/poly(propylene fumarate), chitosan, and combinations thereof.

49. The injection preparation kit of claim 46, further comprising an amount of a second carrier component, wherein the amounts of the first and the second carrier components are packaged separately.

50. The injection preparation kit of claim 49, wherein the first carrier component is thrombin and the second carrier component is fibrinogen.

51. The injection preparation kit of claim 9, further comprising a Y-connector configured to reversibly couple to a multi-barrel delivery syringe, the Y-connector comprising: a connector body having a first end and a second end, the first end defining at least two connector inlets for reversibly coupling the Y-connector to the at least two barrels of the delivery syringe; a dual lumen cannula coupled to the second end of the connector body; and a spinal needle coupled to the dual lumen cannula.

52. The injection preparation kit of claim 24, further comprising a Y-connector configured to reversibly couple to a multi-barrel delivery syringe, the Y-connector comprising: a connector body having a first end and a second end, the first end defining at least two connector inlets for reversibly coupling the Y-connector to the at least two barrels of the delivery syringe; a dual lumen cannula coupled to the second end of the connector body; and a spinal needle coupled to the dual lumen cannula.

53. The injection preparation kit of claim 37, further comprising a light conduit for delivering light from a light source to at least the first carrier component.

54. The injection preparation kit of claim 46, further comprising a light conduit for delivering light from a light source to at least the first carrier component.

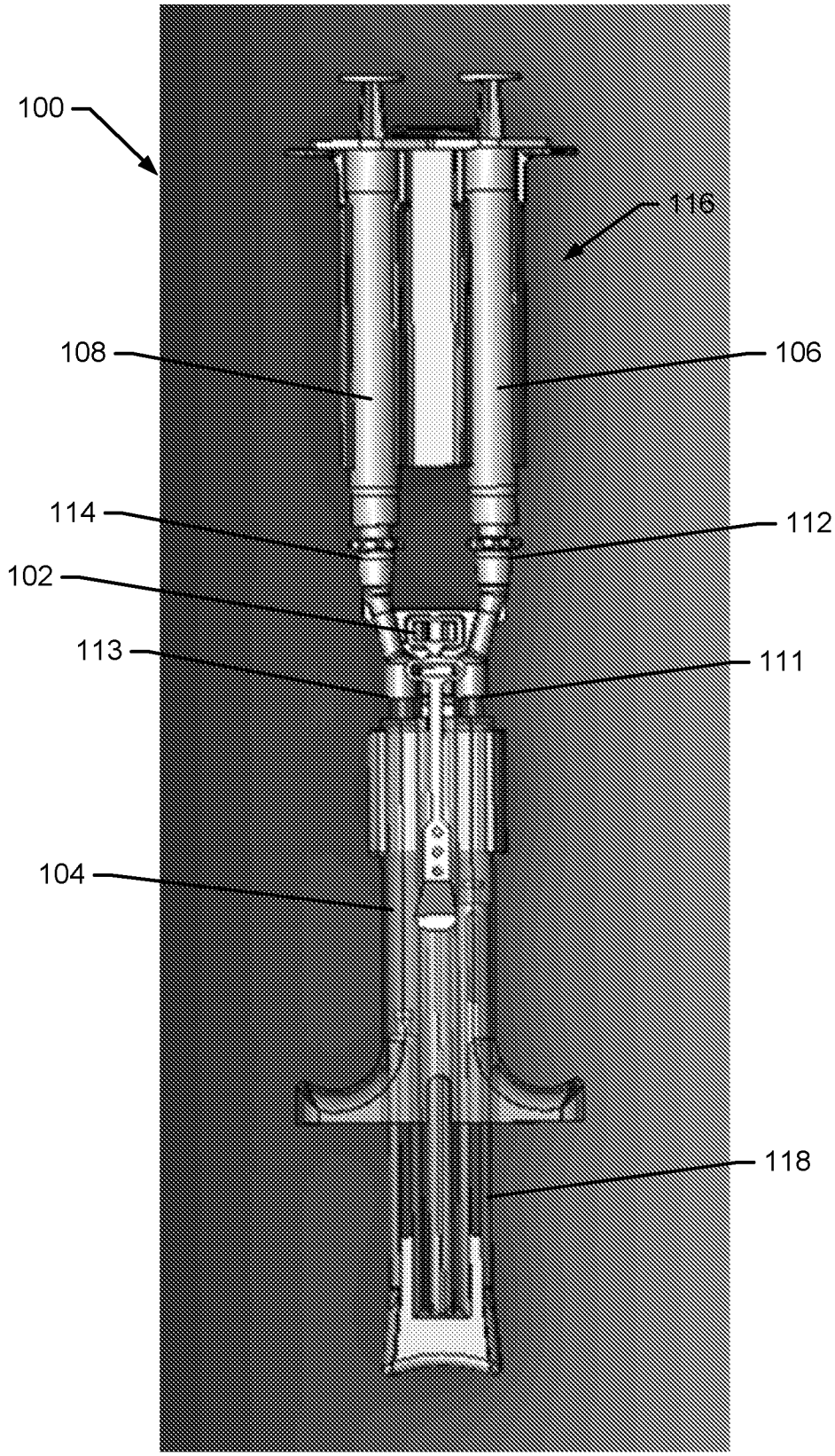
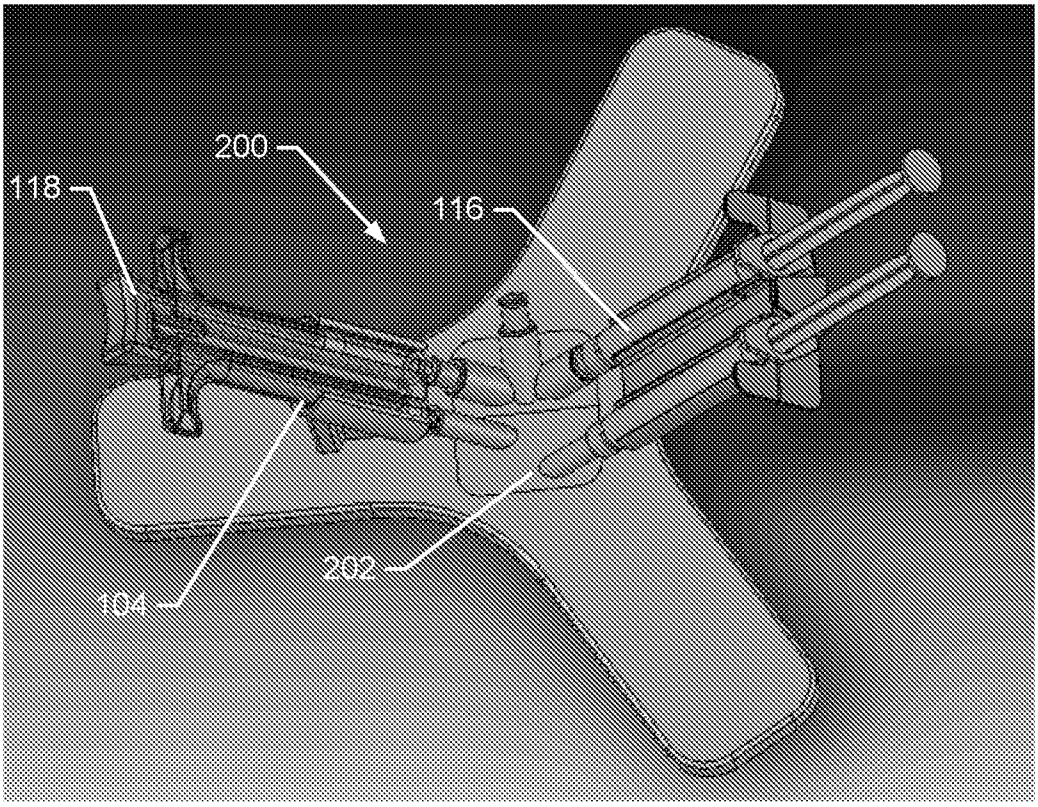


FIG. 1

A.


200
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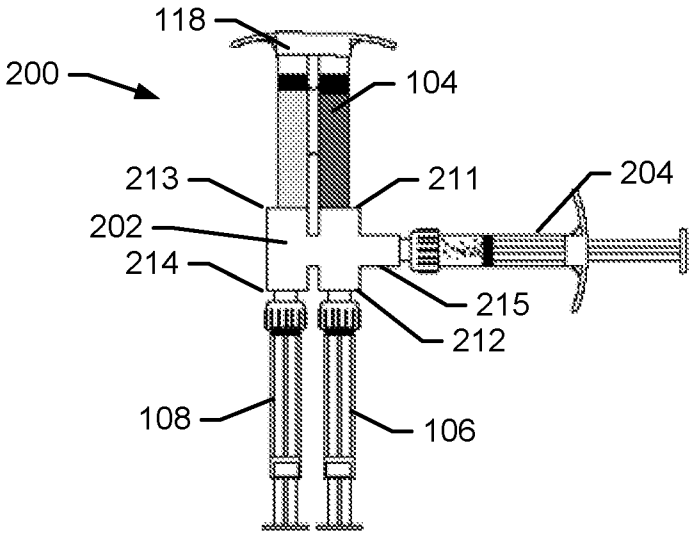
116
104
202

B.


118
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212
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106

FIG. 2

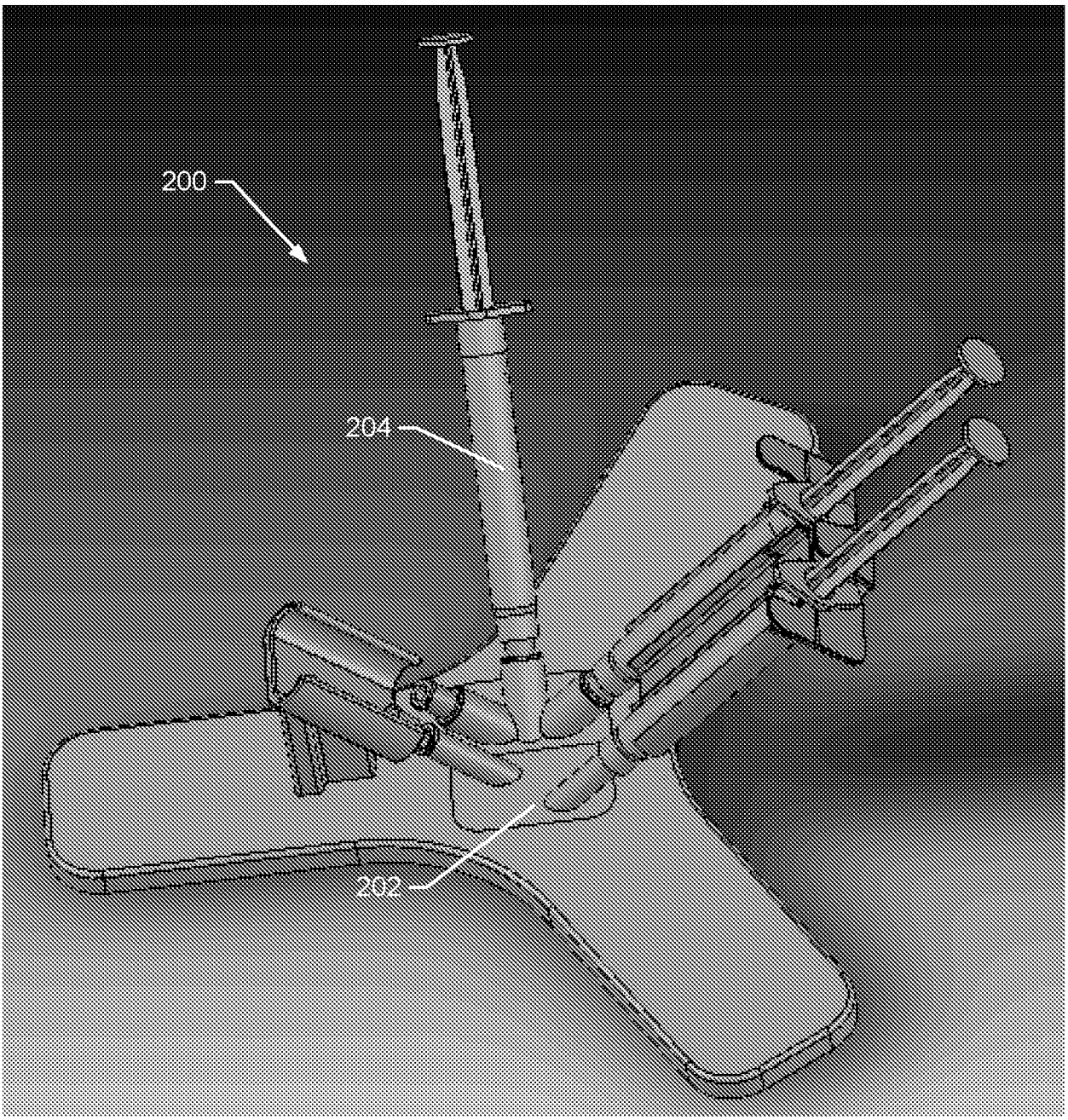
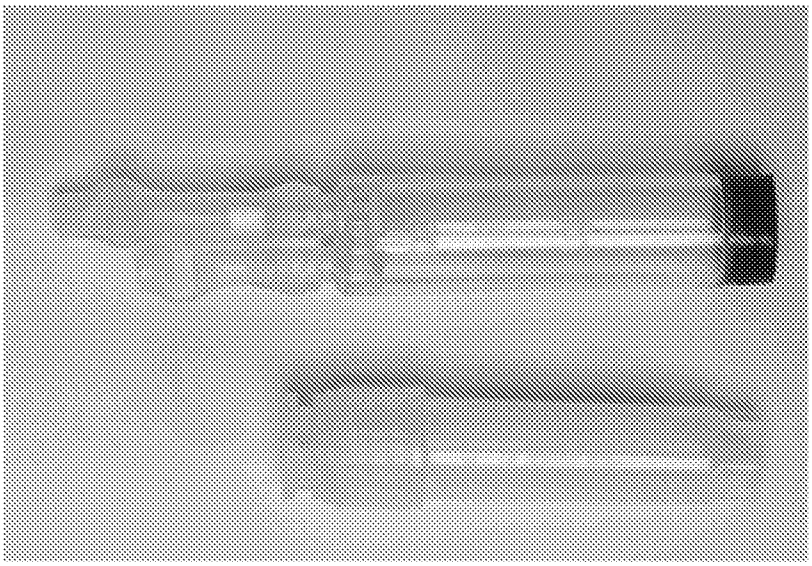
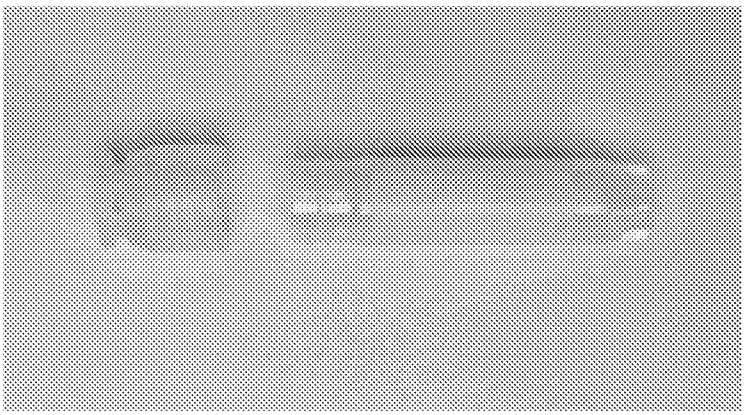


FIG. 3

A.



B.



C.

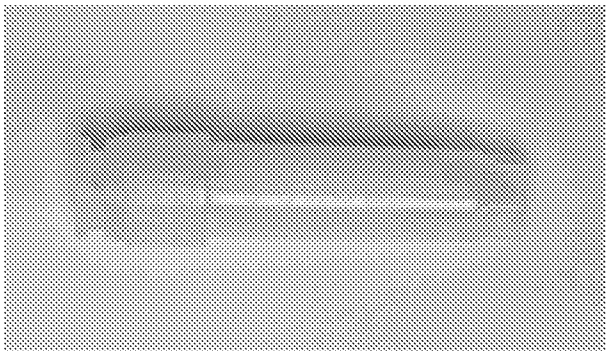


FIG. 4

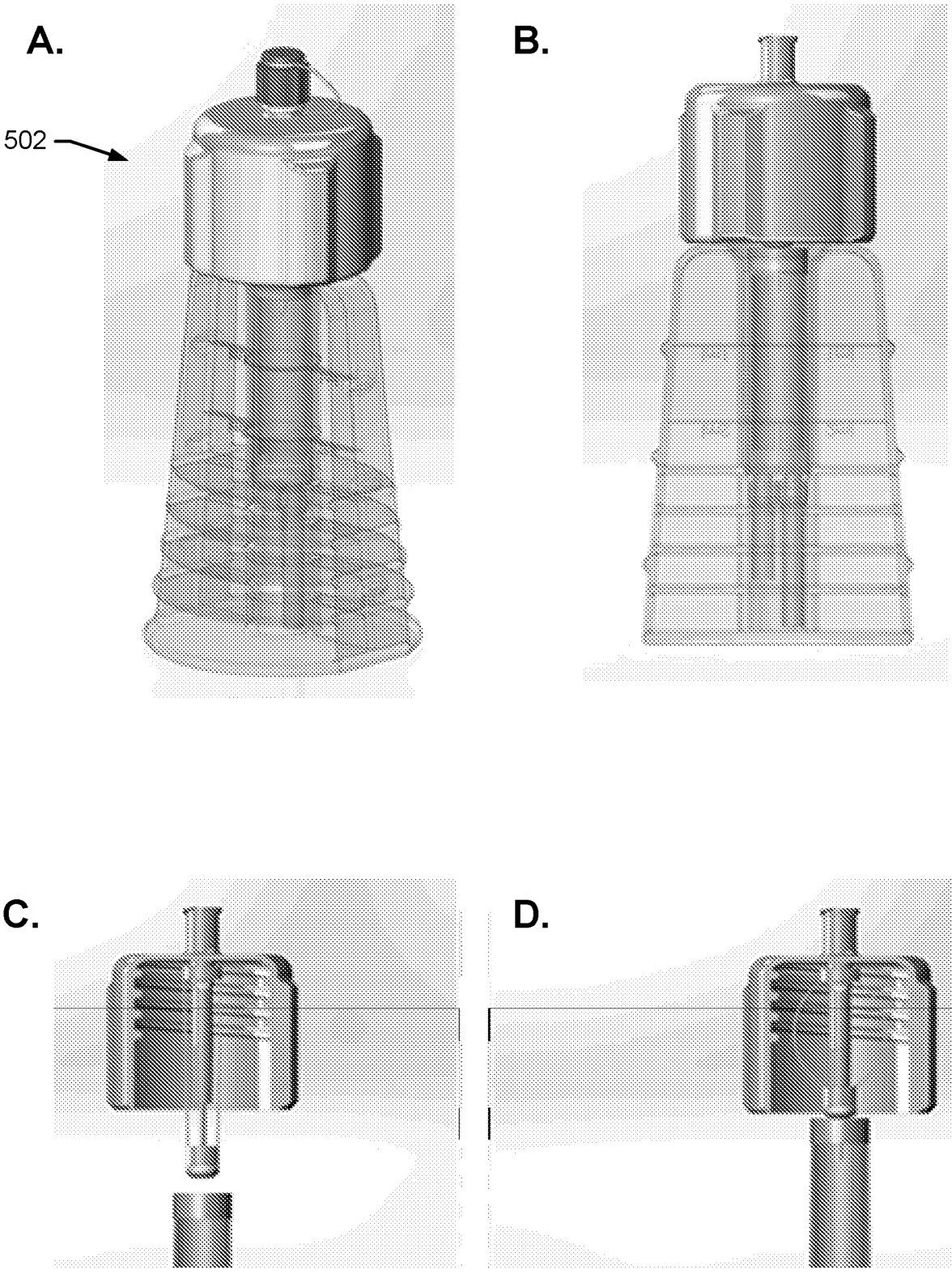


FIG. 5

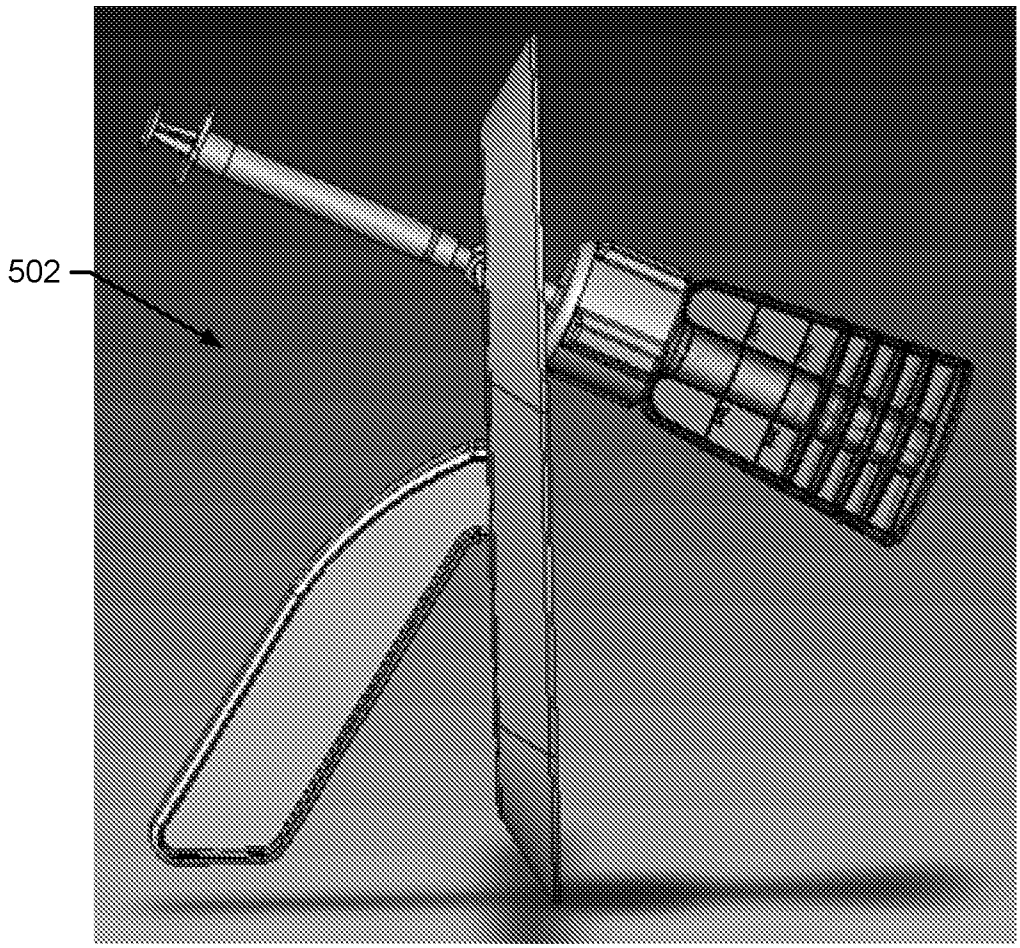


FIG. 6

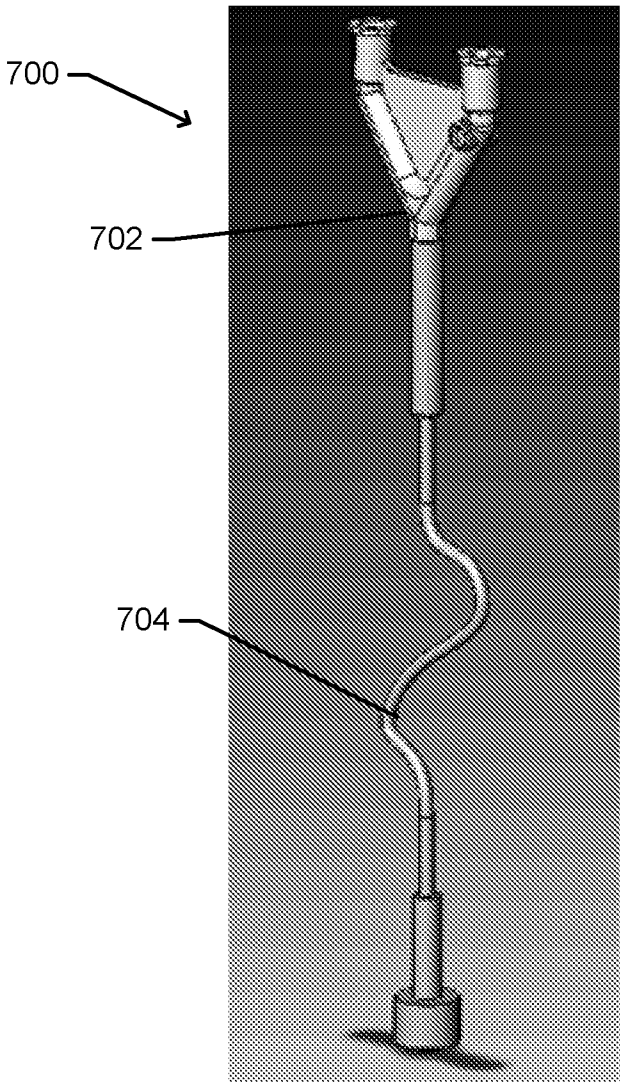


FIG. 7

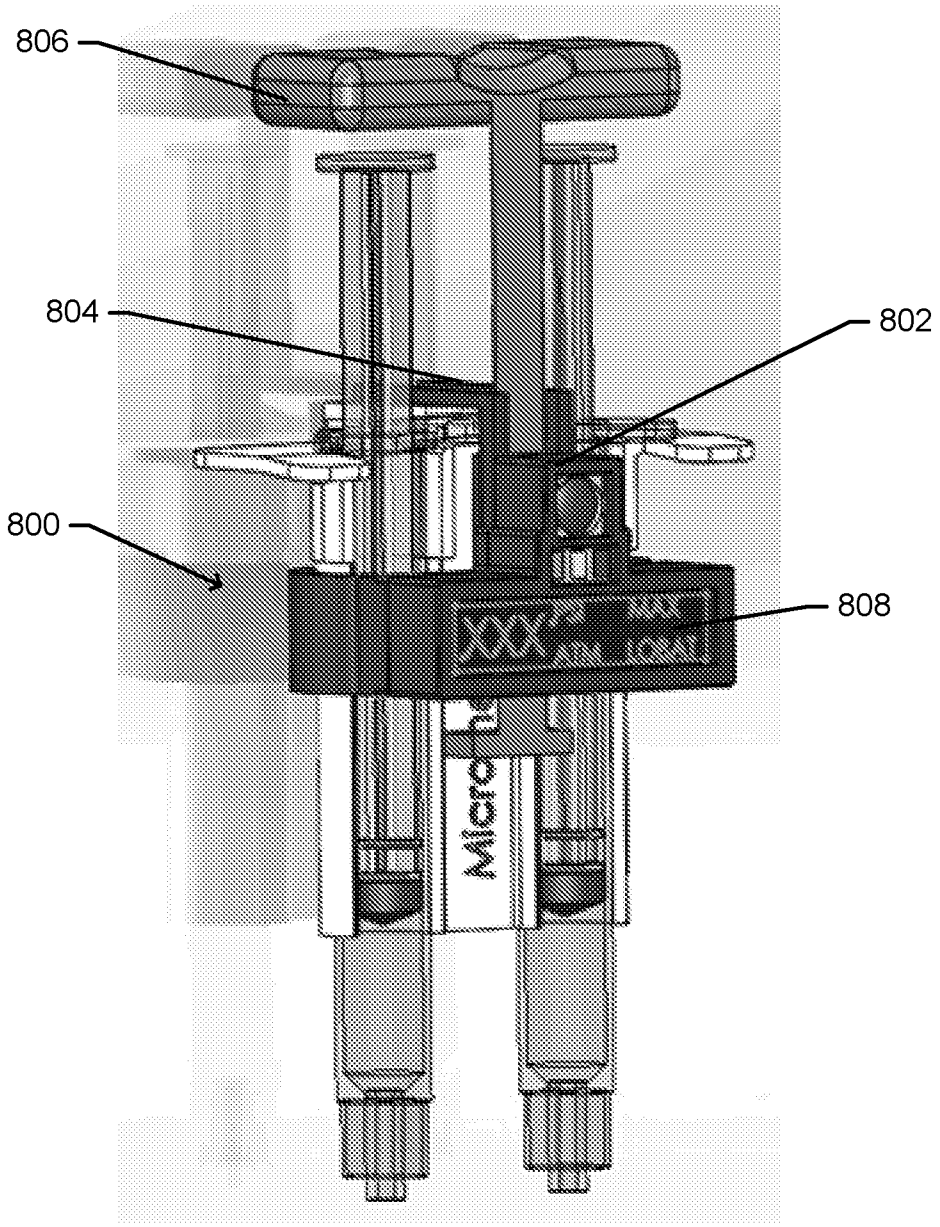
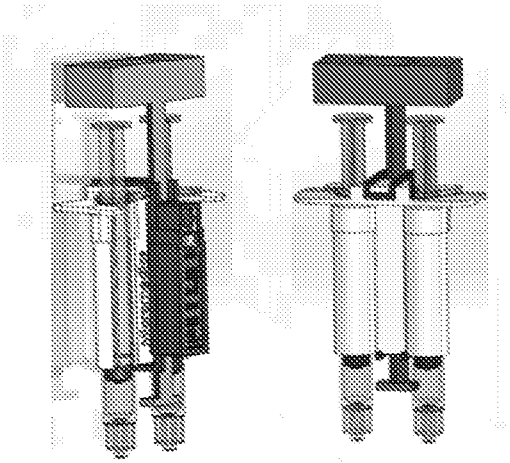
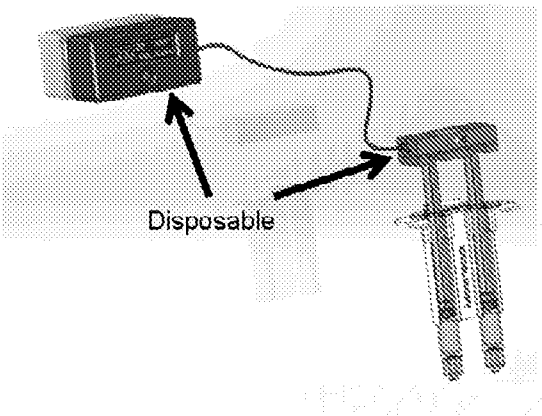


FIG. 8

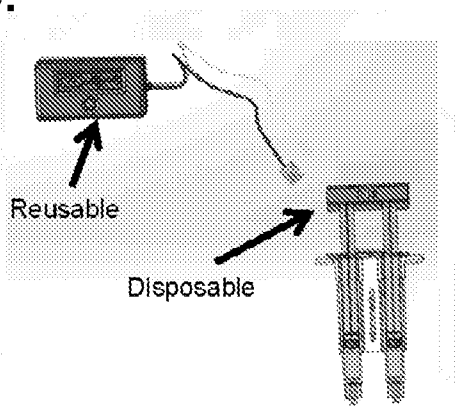
A.



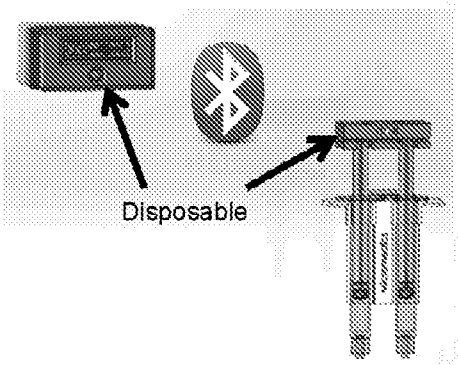
B.


Disposable

C.


Reusable
Disposable

D.


Disposable

E.

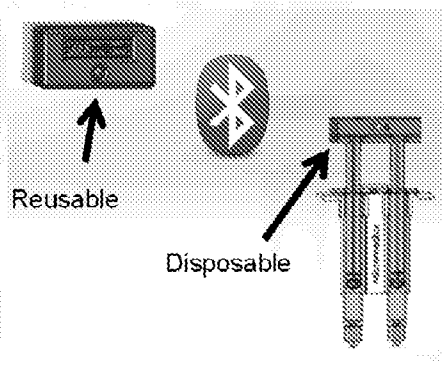
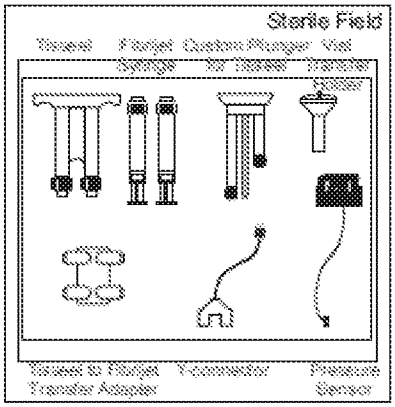
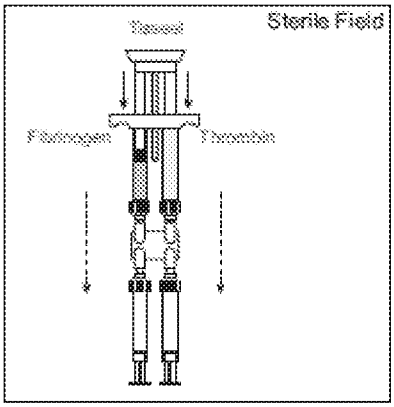

Reusable
Disposable

FIG. 9

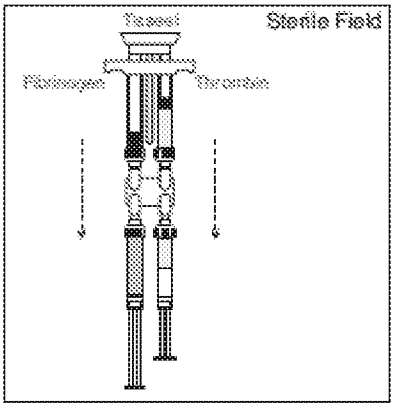
All fluids are colorless. Colors shown here to illustrate contents.



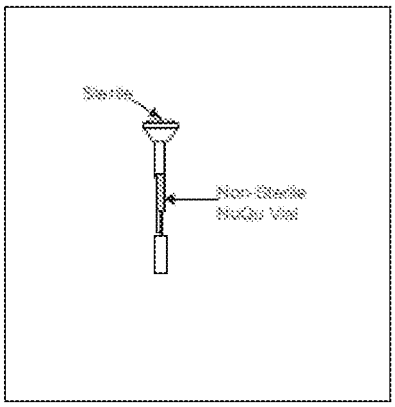
Prepare sterile field (Treatment Prep Kit, Pressure Device, Intradiscal Kit).



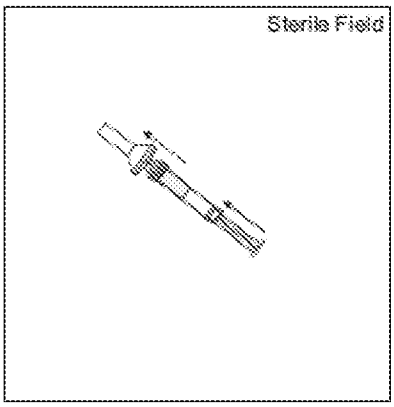
Connect Tisseal and Delivery Syringes to Transfer Hub



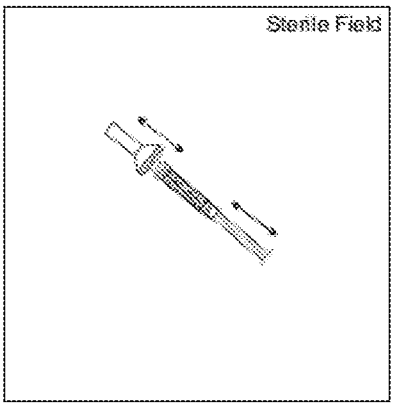
Transfer Tisseal to Delivery Syringes.



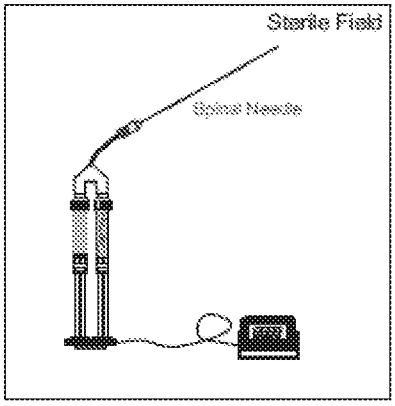
Insert NuQu vial into holder.



Transfer Thrombin into NuQu Cell Vial

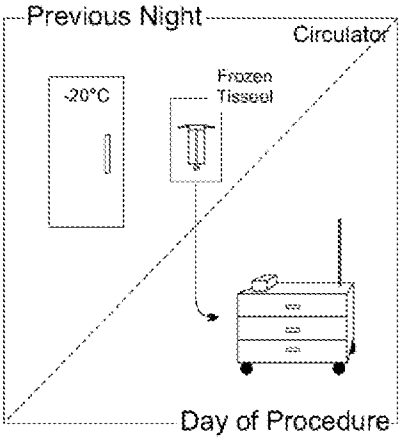


Mix Thrombin and NuQu Cells through gentle agitation and transfer back to syringe.

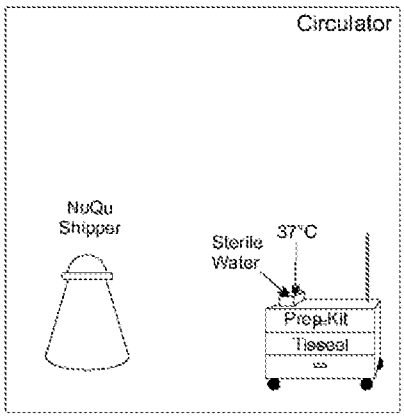


Connect Blending Connector and Pressure Sensor

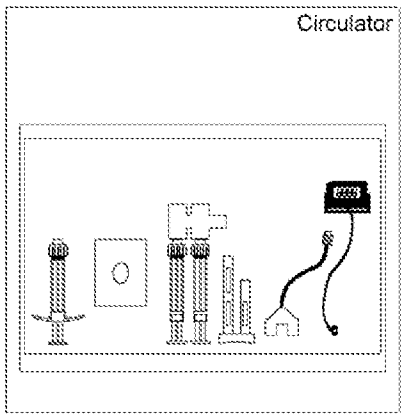
FIG. 10



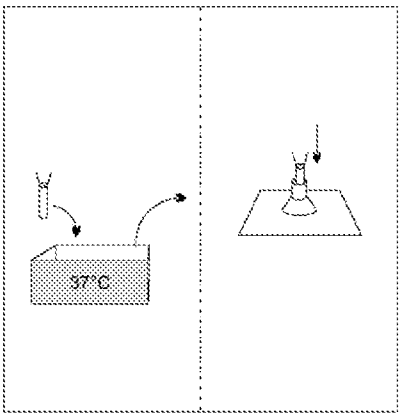
Thaw Tisseel over night.



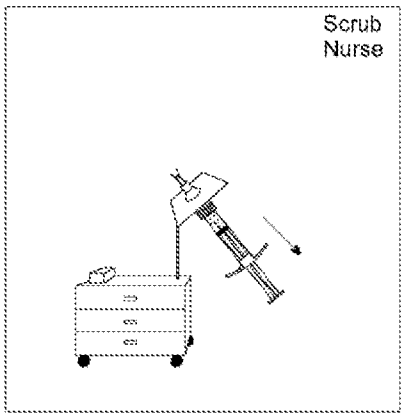
Gather equipment / materials (Procedure cart, -80°C Shipper). Prepare water bath.



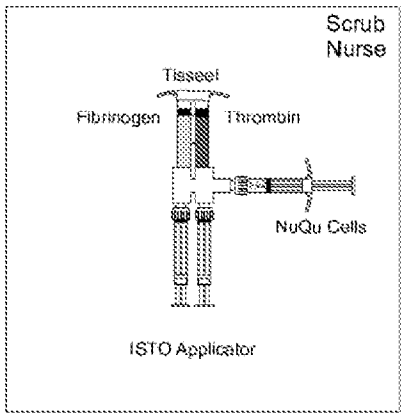
Prepare sterile field (Treatment Prep Kit, Pressure Device, Intradiscal Kit).



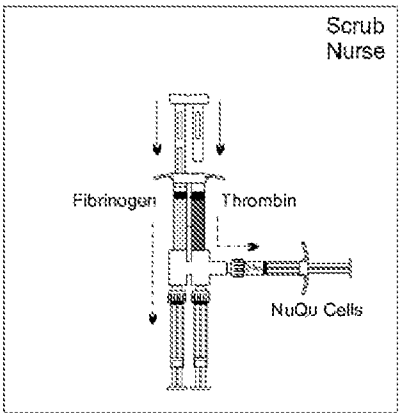
Thaw NuQu Cells
Attach Transfer Shield



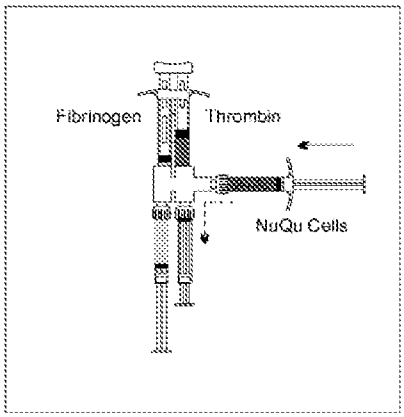
Load NuQu Cells into Transfer Syringe



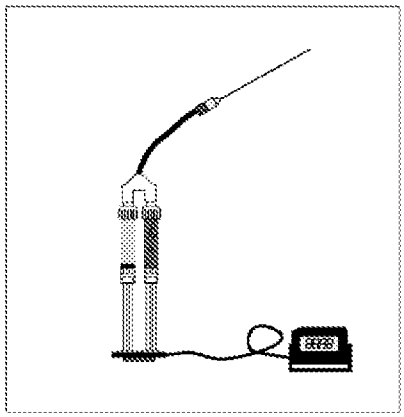
Connect NuQu Transfer Syringe and Tisseel to Custom Coupler



Transfer Tisseel using custom ram rod



Transfer NuQu Cells and Thrombin to ISTO Applicator



Connect Blending Connector and Pressure Sensor

FIG. 11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/43522

A. CLASSIFICATION OF SUBJECT MATTER
IPC - A61M 5/20, 5/48, 5/168 (2017.01)
CPC - A61M 5/20, 5/2066, 5/486, 5/16827

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2007/0213660 A1 (RICHARDS, M et al.) 13 September 2007; Figures 4, 6, and 13; Pargraphs [0055], [0057], [0060], [0062], and [0074]	1, 8-10, 14, 15, 24, 25, 36-41, and 45-52
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Y		2-6, 11, 12, 16-20, 22, 23, 26, 27, 33-35, 42-44, 53, and 54
Y	US 2014/0081208 A1 (MALONEY, M) 20 March 2014; Figures 1 and 3-3B; Paragraphs [0004], [0005], [0024], [0029], [0032], [0034]; Claim 1	2-6 and 16-20
Y	US 2008/0161772 A1 (NAYAK, A et al.) 3 July 2008; Figure 2; Paragraph [0041]	11, 12, 26, and 27
Y	US 2011/0033925 A1 (DUFFY, N et al.) 10 February 2011; Figure 6A; Paragraph [0076]	33-35 and 42-44
Y	US 2003/0181850 A1 (DIAMOND, S et al.) 25 September 2003; Figure 12; Paragraphs [0004] and [0072] - [0074]	22 and 23
Y	US 2009/0118696 A1 (Nyhart, E) 7 May 2009; Figures 2 and 3; Paragraphs [0046], [0047], and [0083]	53 and 54
A	US 2015/0262512 A1 (TRUINJECT MEDICAL CORP.) 17 September 2015; Paragraphs [0011] and [0060]	7 and 21
A	US 2001/0016709 A1 (TOVEY, H et al.) 23 August 2001; Figure 4; Paragraphs [0013], [0041], and [0052]	13 and 28

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

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

Date of the actual completion of the international search	Date of mailing of the international search report
26 October 2017 (26.10.2017)	17 NOV 2017
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/43522

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

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

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

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

3. ☒ Claims Nos.: 31, 32
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I: Claims 1-28, 33-54 are directed toward an injection preparation device.

Group II: Claims 29, 30 are directed toward a transfer shield for use with a cell storage container.

The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons.

-***-See Supplemental Page-***-

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

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

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

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-28, 33-54

Remark on Protest

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

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

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US17/43522

-***-Continued from Box III: Lack of Unity of Invention-***-
The special technical features of Group I include a body configured to reversibly engage a multi-barrel carrier syringe, a cell transfer syringe, a cell delivery syringe and a carrier delivery syringe, the body comprising: a first transfer portion defining a first inlet configured to reversibly couple to a first barrel of the multi-barrel carrier syringe, a second inlet configured to reversibly couple to the barrel of the cell delivery syringe, and a fifth inlet configured to reversibly couple to the barrel of the cell transfer syringe, wherein the first, second, and fifth inlets communicate through a first conduit through the body; and a second transfer portion defining a third inlet configured to reversibly couple to a second barrel of the multi-barrel carrier syringe, a fourth inlet configured to reversibly couple to the barrel of the carrier delivery syringe, wherein the third and fourth inlets communicate through a second conduit through the body; and an injection load monitoring device configured to reversibly couple to a delivery syringe (which is not present in Group II).

The special technical features of Group II include a transfer shield for use with a cell storage container having an opening covered by a sterile seal capable of penetration by a hollow needle, the transfer shield comprising: a body having a first surface and a second surface and defining an opening therethrough from the first surface to the second surface, the opening having a rim; a substantially tubular projection from the first surface defining a wall surrounding the opening; the hollow needle disposed perpendicular to the first surface from within the wall, wherein the hollow needle is coupled to the rim of the opening and the hollow needle has a length less than or equal to a depth of the tubular projection from the first surface (which is not present in Group I).

The common technical features of Groups I and II include a body.

These common technical features are disclosed by US 2014/0081208 A1 (MALONEY): a body (syringe body; paragraph [0005]).

Because the common technical features are disclosed by Maloney, the inventions are not so linked as to form a single general inventive concept. Therefore, Groups I and II lack unity.