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Bioreactor

Abstract

A bioreactor comprising a housing defining a perfusion chamber, the housing including at least one port, wherein the at least one port is coupled to the housing, and a sample holder positioned within the perfusion chamber. A bioreactor and spheroid-based biofabrication method for making perfusible tissue constructs and perfusing them.

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Background/Summary

RELATED APPLICATIONS (1) The present disclosure is a continuation of U.S. Patent Application Ser. No. 16/261,526 filed on Jan. 29, 2018 and is related to and claims priority to U.S. Provisional Application No. 62/623,921, filed Jan. 30, 2018, entitled “BIOREACTOR,” the entire disclosure of which is are hereby expressly incorporated by reference.

FIELD OF DISCLOSURE
(1) The present disclosure relates generally to a bioreactor. In particular, the present disclosure relates to a bioreactor configured to permit tissue construct perfusion and mitigate risks associated with handling and transferring tissue constructs from printing vessels to incubation and/or perfusion vessels.
BACKGROUND OF DISCLOSURE
(2) Bioprinting or biofabrication is used to produce tissue constructs from cells. These tissue constructs are then either investigated as models of tissue development or tissue pathology or prepared as replacements of damaged or destroyed tissues. However, following bioprinting, tissue constructs must often be contained in a system whereby tissues can culture or incubate for days to months and in some cases these tissues need to be perfused with nutrients. In current modes of tissue bioprinting, the tissues must be transferred from the printing vessel to an incubation and/or perfusion vessel, requiring the user to manually handle the tissue construct, which can be dropped or inadvertently contaminated. Thus, it would be beneficial to have a device that mitigates the risks associated with handling and transferring the tissue construct from the printing vessel to the culture/perfusion vessel.
SUMMARY OF THE DISCLOSURE
(3) In one embodiment of the present disclosure, a modular bioreactor is disclosed comprising a housing defining a perfusion chamber, the housing including at least one port, wherein the at least one port is coupled to the housing, a sample holder positioned within the perfusion chamber, detachable modules for applying biological agents to tissues contained within the perfusion chamber at biologically relevant rates in the process of maturing biofabricated tissues, and detachable modules for aseptically ascertaining conditions within the perfusion chamber.
(4) In one embodiment of the bioreactor, the at least one port is an analyzing port configured to receive at least one of a sensor and an imaging device.
(5) In another embodiment of the bioreactor, the at least one of the sensor and the imaging device is one of an optical device and an infrared device.
(6) In a further embodiment of the bioreactor, the at least one port includes a first port and a second port, the first port comprising an inlet port into the housing and the second port comprising an outlet port from the housing.
(7) In another embodiment of the bioreactor, the first port and the second port are integrally formed as a single one-piece structure with the housing.
(8) In a further embodiment of the bioreactor, the bioreactor is part of a system comprising a pump and tubing, wherein a first section of the tubing couples the inlet port to the pump and a second section of the tubing couples to outlet port to the pump.
(9) In another embodiment of the bioreactor, the at least one port further includes a third port, the third port including an analyzing port.
(10) In a further embodiment of the bioreactor, the analyzing port is positioned between the inlet port and the outlet port.
(11) In another embodiment of the bioreactor, the bioreactor further comprises a cover configured to couple with the housing to close off the perfusion chamber from atmosphere.
(12) In another embodiment of the present disclosure, a bioreactor is disclosed comprising a

housing configured to define a perfusion chamber; and a sample holder positioned within the perfusion chamber; wherein the housing includes at least one observation port.
(13) In one embodiment of the bioreactor, the housing further includes a cover configured to couple with the housing to close of the perfusion chamber from the atmosphere, and the at least one observation port is an analyzing portion within the cover.
(14) In another embodiment of the bioreactor, the at least one observation port is an analyzing port positioned within a wall of the housing.
(15) In yet another embodiment of the present disclosure, a bioreactor is disclosed comprising a housing configured to define a perfusion chamber, and a sample holder positioned within the perfusion chamber, the sample holder including a base and a platen configured to be positioned in abutment with the base, wherein the platen includes at least one handling extension.
(16) In one embodiment of the bioreactor, the base includes at least one securing extension configured to hold the platen in abutment with the base.
(17) In another embodiment of the bioreactor, the at least one securing extension includes two separate securing extensions.
(18) In a further embodiment of the bioreactor, the sample holder further includes at least one perfusion opening extending through the base and the platen.
(19) In another embodiment of the bioreactor, the platen further includes a skirt extending from a bottom surface of the platen.
(20) In a further embodiment of the bioreactor, the at least one handling extension includes two handling extension, each of the two handling extensions being positioned to either side of the at least one perfusion opening.
(21) In yet another embodiment of the present disclosure, a method for preparing a tissue construct is disclosed comprising the steps of filling a bioreactor with a fluid, the bioreactor including a housing defining a perfusion chamber, and a sample holder positioned within the perfusion chamber, wherein the housing includes an inlet port and an outlet port, the inlet port and the outlet port being integrally formed as a single one-piece structure with the housing, placing the tissue construct onto the sample holder, and at least one of coupling the inlet port and the outlet port of the bioreactor to a perfusion pump, placing the bioreactor in an incubator, and manipulating the tissue construct within the bioreactor.
(22) In one embodiment of the method, the method further includes observing the tissue construct through at least one observation port within the housing.
(23) In another embodiment of the method, the method further includes transferring the bioreactor to a desired area.
(24) In still another embodiment of the present disclosure, a method for preparing a tissue construct is disclosed comprising the steps of filling a bioreactor with a fluid, the bioreactor including a housing defining a perfusion chamber, and a sample holder positioned within the perfusion chamber, wherein the housing includes at least one observation port, placing the tissue construct onto the sample holder, and observing the tissue constructions through the at least one observation port.
(25) In one embodiment of the method, the housing includes a cover and the at least one observation port is an analyzing portion of the cover.
(26) In another embodiment of the method, the at least one observation port is a port positioned along a wall of the housing.
(27) In a further embodiment of the method, the step of observing the tissue construct can occur simultaneously with the step of printing the tissue construct.
(28) In yet another embodiment of the present disclosure, a bioreactor is disclosed comprising a housing configured to define a perfusion chamber, and a sample holder positioned within the perfusion chamber, the sample holder including a base and a platen configured to be positioned in abutment with the base, wherein the plate and the base include at least one perfusion opening

configured to align with a channel within a tissue construct such that a fluid may be perfused through the base, the platen, and the tissue construct via a single channel.
(29) In one embodiment of the bioreactor, the platen includes a plurality of perfusion openings, and each of a majority of the plurality of perfusion openings is configured to align with one of a plurality of channels within the tissue construct.
(30) In yet another embodiment of the present disclosure, a bioreactor is disclosed comprising a housing configured to define a perfusion chamber, and a sample holder positioned within the perfusion chamber, the sample holder including a base and a platen configured to be positioned in abutment with the base, wherein at least one of the base and the platen includes at least one handling extension, wherein the housing further includes a cover configured to couple with the housing to regulate interaction between the perfusion chamber and the atmosphere, and at least one observation port configured to be an analyzing portion within the cover designed with acoustic properties which facilitate transmission and reception of a plurality of ultrasound signals configured for image formation and ultrasound-based fluid flow measurements to provide an aseptic management of the transmission and reception.
(31) In one embodiment of the bioreactor, the base includes at least one securing extension configured to hold the platen in abutment with the base. In a variation, the at least one securing extension includes two separate securing extensions.
(32) In another embodiment of the bioreactor, the sample holder further includes at least one perfusion opening extending through the base and the platen.
(33) In yet another embodiment of the bioreactor, the platen further includes a skirt extending from a bottom surface of the platen. In a variation, the at least one handling extension includes two handling extension, each of the two handling extensions being positioned to adjacent a side of the at least one perfusion opening.
(34) In still another embodiment of the present disclosure, the plurality of ultrasound signals includes biological and material properties.
(35) In yet another embodiment of the present disclosure, a method for preparing a biologically active tissue construct made from cells and extracellular matrix is disclosed. The method comprises partially or fully filling a bioreactor with a biocompatible fluid, the bioreactor including a housing defining a perfusion chamber, and a sample holder positioned within the perfusion chamber, wherein the housing includes an inlet port and an outlet port, the inlet port and the outlet port being integrally formed as a single one-piece structure with the housing; placing the tissue construct into or onto a module associated with the sample holder; and at least one of: coupling the inlet port and the outlet port of the bioreactor to a perfusion pump, placing the bioreactor in an incubator, and manipulating the tissue construct within the bioreactor to apply at least one of nutritious perfusion and stimuli.
(36) In one embodiment of the method, the method further comprises observing the tissue construct through at least one observation port within the housing. In a variation, the method further comprises transferring the bioreactor to a desired area.
(37) In another embodiment of the method, the method further comprises including in the model, a base and a platen configured to be positioned in abutment with the base. In a variation, the method further comprises including in the housing, a cover and an analyzing portion of the cover.
(38) In yet another embodiment of the method, the method further comprises including the at least one observation port being positioned along a wall of the housing.
(39) In still another embodiment of the method, the method further comprises simultaneously performing observing the tissue construct and printing the tissue construct.
(40) In still yet another embodiment of the method, the method further comprises generating the tissue construct such that the tissue construct is self-supporting and having one or more perfusion channels. In a variation, the method further comprises creating the one or more perfusion channels of the tissue construct using corresponding one or more needles of the platen.

(41) In yet another embodiment of the present disclosure, a perfusible tissue construct capable of supporting the stress of its own weight when unsupported by any other structure or medium other than its own bulk or air is disclosed comprising a body removably attached to a platen configured to be positioned in abutment with a base of a sample holder disposed within a perfusion chamber, which contains a biocompatible fluid sufficient to maintain tissue viability, such that the tissue construct remains in alignment with a plurality of perfusion channels disposed in the tissue construct independent of an intervening non-tissue material penetrating through the tissue construct, wherein the platen and the base include at least one perfusion opening configured to align with at least one of the plurality of perfusion channels such that the fluid is perfused through the base, the platen, and the tissue construct.

(42) In one embodiment of the perfusible tissue construct, at least one of the base and the platen includes a plurality of perfusion openings, each of a majority of the plurality of perfusion openings configured to align with at least one of the plurality of channels disposed in the tissue construct.

(43) In another embodiment of the perfusible tissue construct, the sample holder includes a construct support configured to removably attach the body of the tissue to the platen. In a variation, the construct support includes an adhesive interface.

(44) In yet another embodiment of the perfusible tissue construct, the tissue construct is capable of supporting its own weight without the support of any intervening mechanical support.

(45) In yet another embodiment of the present disclosure, a bioreactor is provided that includes a platen containing a tissue construct is temporarily coupled to a base. The base is temporarily or removably coupled to a sample holder within a perfusion chamber. The bioreactor further includes a sample holder positioned within the perfusion chamber. The sample holder includes the base and a platen configured to be positioned in abutment with the base, wherein the platen and the base include at least one perfusion opening configured to align with a channel within the tissue construct such that a fluid can be perfused through the base, the platen, and the tissue construct via a single channel.

(46) In yet another embodiment of the present disclosure, a method for biofabricating scaffold-free tissues is provided wherein a final biofabricated tissue is capable of supporting its own weight without the support of any intervening mechanical support. In one example, the biofabricated tissue can be perfused or otherwise supplied with nutrients during and following maturation.

(47) In yet another embodiment of the present disclosure, a bioreactor is provided that includes a tissue adhered to a platen having a plurality of microchannels aligned with microchannels in the tissue.

(48) In yet another embodiment of the present disclosure, a method for biofabricating tissues is provided. The method includes positioning a platen-sleeve subassembly having a platen and a sleeve into a cast mold; placing cellular spheroids into the platen-sleeve subassembly, the platen-sleeve subassembly being temporarily or removably coupled to the cast mold; contacting the spheroids with a floor of the platen to be adhered to or otherwise secured to the floor; allowing a passage of nutrients and media using an interface between the platen and walls of the platen (e.g., sleeve); fusing the spheroids with the platen to one another; removing the platen-sleeve assembly from the cast mold after a predetermined fusion period; placing the platen-sleeve assembly onto a perfusion module and placing the perfusion module in a perfusion chamber of a bioreactor; creating a negative volume when the cast mold is removed to generate channels in the resulting biofabricated tissue which are intrinsically aligned with perfusion openings in the platen such that a fluid can be perfused through the platen and the tissue construct; and generating a self-supporting tissue which is adhered to the platen having perfusion channels aligned with perfusion channels in the tissue construct without using intervening non-tissue materials penetrating through the tissue construct.

(49) In yet another embodiment of the present disclosure, a device to fill space within a perfusion chamber, thereby reducing a volume needed to fill the perfusion chamber with medium (e.g., a

space saver). In one example, bioreactor and mold components are designed to remain sterile during a handling possess such that the device can be aseptically handled with forceps. In another example, a perfusion bioreactor is designed to fit within the confines of standard cell culture equipment such as plate holders and automated biomaterial handling systems.

(50) Additional features and advantages of the present invention will become apparent to those skilled in the art upon consideration of the following detailed description of the illustrative embodiment exemplifying the best mode of carrying out the invention as presently perceived.

Description

BRIEF DESCRIPTION OF THE DRAWINGS

(1) The foregoing aspects and many of the intended advantages of this disclosure will become more readily appreciated as the same becomes better understood by reference to the following detailed description when taken in conjunction with the accompanying drawing.

(2) FIG. **1** shows a perspective view of an embodiment of a bioreactor of the present disclosure including an inlet port and an outlet port;

(3) FIG. **2** shows a perspective view of another embodiment of a bioreactor of the present disclosure including an inlet port, an outlet port, and an observing/analyzing port;

(4) FIG. **3** shows a sectioned perspective view of the bioreactor of FIG. **2**;

(5) FIG. **4** shows a diagram of an embodiment of a system of the present disclosure including a bioreactor and a pump;

(6) FIG. **5** shows a semi-transparent top view of the bioreactor of FIG. **2**;

(7) FIG. **6** shows an exploded view of a mount for a sensor or an imaging device coupled to an observing/analyzing port of the bioreactor of FIG. **2**;

(8) FIG. **7** shows the bioreactor of FIG. **2** with an embodiment of a cover of the present disclosure;

(9) FIG. **8** shows the bioreactor of FIG. **2** with another embodiment of a cover of the present disclosure including an analyzing portion;

(10) FIG. **9** shows a sectioned view of the bioreactor and the cover of FIG. **8**;

(11) FIG. **10** shows a perspective view of an embodiment of a sample holder of the present disclosure having a base and a platen;

(12) FIG. **11** shows a sectioned view of the sample holder of FIG. **10**;

(13) FIG. **12** shows a perspective view of the platen of the sample holder of FIG. **10**;

(14) FIG. **13** shows a cross-sectional view of the platen of FIG. **12**;

(15) FIG. **14** shows a perspective view of another embodiment of a sample holder of the present disclosure;

(16) FIG. **15** shows a front semi-transparent view of the sample holder of FIG. **14**;

(17) FIG. **16** shows a top perspective view of a platen of the sample holder of FIG. **14**, the platen including handling extensions;

(18) FIG. **17** shows a bottom perspective view of the platen of FIG. **16**;

(19) FIG. **18** shows a perspective view of an embodiment of a printing sample holder of the present disclosure;

(20) FIG. **19** shows a top view of the printing sample holder of FIG. **18**;

(21) FIG. **20** shows a sectioned view of the printing sample holder of FIG. **18**;

(22) FIG. **21** shows a perspective view of a tissue construct and a platen of the printing sample holder of FIG. **18** being removed from a base of the printing sample holder of FIG. **18**;

(23) FIG. **22** shows a perspective view of a platen-sleeve subassembly of the present disclosure including a sleeve and a platen;

(24) FIG. **23** shows a perspective view of the platen-sleeve subassembly of FIG. **22** without the sleeve;

(25) FIG. **24** shows a cross-sectional view of the platen-sleeve subassembly of FIG. **23**;
(26) FIG. **25** shows a perspective view of a cast mold used with the platen-sleeve subassembly of FIG. **22**;
(27) FIG. **26** shows a perspective view of the cast mold of FIG. **25** having the platen-sleeve subassembly of FIG. **22**;
(28) FIG. **27** shows an exploded view of the cast mold of FIG. **26**;
(29) FIG. **28** shows a perfusion module of the present disclosure having the platen-sleeve subassembly of FIG. **22**; and
(30) FIG. **29** shows a flow chart of a method for biofabricating a scaffold-free tissue in accordance with embodiments of the present disclosure.
(31) Although the drawing represents an embodiment of various features and components according to the present disclosure, the drawing is not necessarily to scale and certain features may be exaggerated in order to better illustrate and explain the present disclosure. The exemplification set out herein illustrates embodiments of the disclosure, and such exemplifications are not to be construed as limiting the scope of the disclosure in any manner.
DETAILED DESCRIPTION
(32) For the purposes of promoting an understanding of the principals of the disclosure, reference will now be made to the embodiment illustrated in the drawing, which is described below. The embodiments disclosed below are not intended to be exhaustive or limit the disclosure to the precise form disclosed in the following detailed description. Rather, the embodiments are chosen and described so that others skilled in the art may utilize their teachings. It will be understood that no limitation of the scope of the disclosure is thereby intended. The disclosure includes any alterations and further modifications in the illustrative devices and described methods and further applications of the principles of the disclosure which would normally occur to one skilled in the art to which the disclosure relates.
(33) A bioreactor is disclosed for three-dimensional bioprinting, incubating, manipulating, perfusing, and/or observing/analyzing tissue constructs. Referring to FIGS. **1-3**, a bioreactor **10** of the present disclosure comprises a housing **100** defining a perfusion chamber **105** and a sample holder **200** positioned within perfusion chamber **105**. In general, bioreactor **10** is configured to house a tissue construct **101** within perfusion chamber **105** such that tissue construct **101** can be analyzed, manipulated, transferred and/or incubated without removing construct **101** from bioreactor **10**. In various embodiments, bioreactor **10** is 3D-printed with material that is biocompatible and/or can be sterilized to further reduce the risk of contamination of perfusion chamber **105** and tissue construct **101**.
(34) With reference to FIGS. **1-5**, housing **100** of bioreactor **10** comprises a lower housing **102** that defines a perfusion chamber **105** within which tissue constructs **101** can be placed on sample holder **200** and incubated, perfused, transferred, manipulated, and/or observed/analyzed. Lower housing **102** includes a front wall **104**, a back wall **106**, a first side wall **107**, a second side wall **108**, and a bottom **109**. In various embodiments, lower housing **102** includes at least one port **110**. The at least one port **110** may, in various embodiments, be integrally formed as a single one-piece structure with lower housing **102**. The at least one port **110** may be formed on any of walls **104**, **106**, **107**, or **108**. The at least one port **110** may include an inlet port **112**, an outlet port **114**, and/or an observing/analyzing port **116**. For example, in one embodiment, the at least one port **110** may include only observing/analyzing port **116**, while in another embodiment, the at least one port may include only inlet port **112** and outlet port **114**. In yet another embodiment, the at least one port may include all of ports **112**, **114**, and **116**.
(35) When housing **100** includes only inlet port **112** and outlet port **114**, ports **112** and **114** may be spaced apart such that each port is closer to the adjacent walls, or ports **112** and **114** may be relatively close to one another and spaced apart from the adjacent walls. In various embodiments, inlet port **112** and outlet port **114** may be on separate walls of lower housing **102**. For example,

inlet port **112** may be positioned along front wall **104**, while outlet port is positioned alongside wall **107** or **108** or back wall **106**.
(36) Referring now to FIGS. **3-5**, in various embodiments, inlet port **112** and outlet port **114** are generally configured to couple to a pump **120** via tubing **121**. By coupling lower housing **102** to pump **120**, tissue construct **101** can be perfused with various fluids. The fluids generally circulated through lower housing **102** and perfusion chamber **105**, and therefore perfused through tissue construct **101**, include water, drug solutions, imaging solutions, nutrient enriched culture media such as blood of various source (i.e., animal or human), cell culture medium (CCM), or Dulbecco's modified eagle medium (DMEM), for example, or other similar fluids. In various embodiments, bioreactor **10** may be positioned within an incubator (not shown) and coupled to a pump **120** with connection tubes **121** coupling ports **112** and **114** of bioreactor **10** to pump **120**. In addition, pump **120** may also be positioned within an incubator (not shown). In various embodiments, pump **120** may be a peristaltic pump or other similar pumps.
(37) In order for the fluid to perfuse tissue construct **101**, lower housing **102** includes an inlet flow channel **122** and an outlet flow channel **124** for directing the flow of the fluid through tissue construct **101**. With reference to FIGS. **3** and **5**, inlet flow channel **122** begins at inlet port **112** and extends thru bottom **109** of lower housing **102** until it is below sample holder **200** and tissue construct **101**. This positioning allows the fluid to be directed through tissue construct **101** from the bottom of construct **101** to the top of construct **101** and then flow out into perfusion chamber **105**. In various embodiments, inlet flow channel **122** may extend inward from inlet port **112** and make a 90 degree turn towards sample holder **200** and the bottom of construct **101**.
(38) Still referring to FIGS. **3** and **5**, outlet flow channel **124** includes an inlet **125** provided along an upper surface **129** of bottom **109** of lower housing **102** and extends from inlet **125** to outlet port **114** such that fluid can be received from within perfusion chamber **105** and directed out of perfusion chamber **105** through outlet port **114**. In various embodiments, inlet **125** is positioned proximate to sample holder **200** such that outlet flow channel **124** extends towards side **107** or **108** of housing **102** and then toward outlet port **114**. The width of inlet flow channel **122** and outlet flow channel **124** may be varied during manufacturing depending on the desired flow velocity or volumetric flow rate required or other various characteristics.
(39) With reference now to FIGS. **2**, **3**, and **6**, observation/analyzing port **116** allows a user to observe or analyze tissue construct **101** during and/or after placing tissue construct **101** within perfusion chamber **105**. Observation/analyzing port **116** may support various sensors or imaging devices. Exemplary sensors or imaging devices may include a camera, an IR device, an ultrasound Doppler probe, or other similar sensors or imaging devices. In general, the sensor or imaging device is coupled to observation/analyzing port **116** of lower housing **102** via a mounting apparatus **134**. Mounting apparatus **134** generally includes a device support **136**, a coupling mount **138** for coupling device support **136** to lower housing **102**, a lens **140**, and a gasket **142**. In various embodiments, gasket **142** is positioned between lens **140** and lower housing **102**, and lens **140** is positioned between coupling mount **138** and gasket **142**.
(40) Referring now to FIGS. **7-9**, in various embodiments, housing **100** of bioreactor **10** may further include a cover **130**. Cover **130** is configured to couple with lower housing **102** such that perfusion chamber **105** is sealed from the atmosphere, and infiltration of pathogens into chamber **105** and tissue construct **101** is prevented. In various embodiments, cover **130′** may include an observing/analyzing portion **132**, such as a window. Observing/analyzing portion **132** may be opaque or transparent, and may be formed of silicon or any other similar opaque or transparent materials. Observing/analyzing portion **132** is generally configured to facilitate transmission of a signal from sensors, such as an ultrasound Doppler probe, a camera, an IR device, or other similar sensors, into perfusion chamber **105** such that tissue construct **101** can be observed, analyzed and/or manipulated within perfusion chamber **105**. For example, the ultrasound Doppler probe can be used to analyze, and therefore, control fluid flow characteristics, such as flow velocity and

turbulent flow, for example, through observing/analyzing portion **132** such that a user has the ability to control cell differentiation and subsequent tissue formation aseptically in real-time. In addition, a camera may be used to observe tissue construct **101** aseptically and in real-time during perfusion and/or incubation. Furthermore, in various embodiments, cover **130** may be a linear actuation module or other modular component configured to provide shear, compressive, tensile and/or cyclic stress or strain or other manipulation to tissue construct **101** to simulate natural tissue activity aseptically in real-time.

(41) Referring now to FIGS. **10-17**, sample holder **200** generally includes a base **202** and a platen **204**, where base **202** includes a perfusion channel **206** and platen **204** includes at least one perfusion opening **207**. In various embodiments, platen **204** may be formed of a biomaterial that facilitates direct cell adhesion, while in other various embodiments, sample holder **200** may further include a construct support **208**. Platen **204** and/or construct support **208** are configured to support tissue construct **101** such that perfusion opening(s) **207** of platen **204** align with at least one of perfusion channel(s) **216** in tissue construct **101**. In general, platen **204** is stacked on base **202** such that a bottom surface of platen **204** abuts a top surface of base **202**, and perfusion channel **206** within base **202** aligns with perfusion opening(s) **207** of platen **204** and at least one of perfusion channel(s) **216** of tissue construct **101** to supply fluid through platen **204** and tissue construct **101**. In various embodiments, construct support **208** includes an adhesive interface, such as collagen, tissue adhesive, gelatin, or other similar materials, applied to an upward-facing surface of platen **204**. The adhesive interface allows cells of tissue construct **101** to adhere to platen **204**. In embodiments, base **202** can be a module which holds platen **204** containing tissue construct **101**. In various embodiments, sample holder **200** is inserted in a space defined by upper surface **129** of bottom **109** of lower housing **102** (FIG. **3**) such that the module having base **202**, platen **204** and tissue construct **101** is secured in the space.

(42) With reference to FIGS. **10**, **11**, **14**, and **15**, in various embodiments, platen **204** is held in abutment with base **202** of sample holder **200** by securing extensions **210** extending upward from base **202**. Securing extensions **210** are configured to further hold platen **204**, and thus tissue construct **101**, in place to allow fluid to perfuse through tissue construct **101** without displacing platen **204**. When sample holder **200** includes securing extensions **210** on base **202**, platen **204** may be removed from base **202** by sliding platen **204** horizontal out from under securing extensions **210** or snapping platen **204** from under securing extensions **210**.

(43) Referring to FIGS. **14-17**, platen **204*** may also, in various embodiments, have handling extensions **212**. Handling extensions **212** extend upward from an upper surface of platen **204***, and allow a user to handle or remove platen **204***, and thus tissue construct **101**, from sample holder **202*** when desired. Furthermore, in various embodiments, platen **204*** may further include a skirt **214** extending from a bottom surface of platen **204***. Skirt **214** allows platen **204*** to better couple with base **202*** such that a fluid tight seal may be formed between platen **204*** and base **202***.

(44) In operation, a single piece of tubing **121** is generally first coupled to inlet port **112** and outlet port **114** of bioreactor **10** to maintain sterility and avoid contamination of the medium/fluid and tissue construct **101**. Subsequently, a fluid, such as nutrient enriched culture medium or other various fluids discussed above, is poured into perfusion chamber **105** and tubing **121** and tissue construct **101** is placed within bioreactor **10**. In various embodiments, tissue construct **101** may be placed within bioreactor **10** before or after the fluid is poured into bioreactor **10**. Tissue construct **101** may be placed within bioreactor **10** by either placing platen **204** with a bioprinted tissue construct **101** adhered thereto within perfusion chamber **105** of bioreactor **10** or printing tissue construct **101** directly into perfusion chamber **105** of bioreactor **10**. Tissue construct **101** may be printed via any various bioprinting method, for example via scaffold-free or scaffold dependent methods (e.g., Kenzan method, centrifugation, molding method, magnetic bioprinting, inkjet printing, laser assisted bioprinting, freeform reversible embedding of suspended hydrogels (FRESH) bioprinting, layer-by-layer bioprinting, modular-assembly bioprinting, automated

assembly, manual assembly, cell self-assembly, extrusion), or via any other bioprinting method.
(45) With reference to FIGS. **18-21**, tissue construct **101** may be printed onto a printing sample holder **218**. In various embodiments, printing sample holder **218** may be positioned within bioreactor **10** which is placed within a bioprinter (not shown). In general, printing sample holder **218** includes a base **220**, a first platen **221**, and a second platen **222**. In various embodiments, platen **222** may be the same as platen **204** such that platen **222** can be used with printing sample holder **218** and removed and coupled to base **202** of sample holder **200**. Printing sample holder **218** may include a flat surface and/or various structures, such as needles, poles, or stumps **224**, for example, which are capable of creating channels **216** within construct **101** once removed. Structures **224** are generally coupled to first platen **221** and extend through openings within second plate **222** such that when second platen **222** is removed from base **220** and first platen **221**, tissue construct **101** is removed from structures **224** creating microchannels **216** within tissue construct **101** (see FIG. **21**).
(46) Once tissue construct **101** is placed within bioreactor **10**, bioreactor **10** may be transported to a desired area, coupled to a pump **120** and/or tissue construct **101** may be analyzed, manipulated and/or observed. In various embodiments, lid **130** may be placed onto lower housing **102** sealing off perfusion chamber **105** before, during or after bioreactor **10** is transferred.
(47) The desired area for bioreactor **10** to be transferred to may, in various embodiments, include a countertop where bioreactor **10** can be coupled to a pump **120** such that fluid/medium can be perfused through tissue construct **101**. In other various embodiments, the desired area may be an incubator (not shown) where tissue construct **101** can be incubated without removing the bioprinted tissue construct **101** from perfusion chamber **105**. In yet other various embodiments, bioreactor **10** may be placed in an incubator and coupled to pump **120** via tubing **121** such that tissue construct **101** can be perfused and incubated concurrently. In various other embodiments, bioreactor **10** may be transferred to a workspace where construct **101** can be further manipulated within chamber **105** prior to or following placement in the incubator. The workspace may include a cell and tissue culture hood, a biosafety cabinet, or other various sterile atmospheres. Being able to transport, perfuse, manipulate, and/or incubate the tissue construct **101** without removing it from bioreactor **10**, allows a user to mitigate the risks associated with handling tissue construct **101** and transferring tissue construct **101** from the printing vessel to the culture/perfusion vessel.
(48) In various embodiments, cameras with or without visible light, Doppler capable ultrasound probes, or other observing or analyzing devices and sensors may be either coupled to analyzing port **116** or operated through window **132** to image, analyze, or otherwise stimulate tissue construct **101**. Observing the construct during printing and/or incubation post-printing, allows a user to properly stimulate or perfuse tissue construct **101** to better duplicate the stimulation and perfusion required by the specific tissue it is replacing. Observing the construct **101** also allows a user to track construct **101** behavior in real-time and over an extended period of time. In addition, the modular nature of bioreactor **10** allows different imaging devices or other sensors to be fitted to the bioreactor **10** while maintaining sterility.
(49) Referring now to FIGS. **22-23**, in various embodiments, a platen-sleeve subassembly **2200** can be used as another sample holder. In FIG. **22**, platen-sleeve subassembly **2200** includes a sleeve **2202** and a platen **2204**. In embodiments, sleeve **2202** has a quadrilateral shape including four side walls **2206** and at least two of side walls **2206** has handling extensions **2208** extending upward from an upper surface of sleeve **2202** for allowing a user to handle or remove sleeve **2202** from platen-sleeve subassembly **2200**. Similarly, platen **2204** has a quadrilateral shape including four sides **2210** and at least two handling extensions **2212** extending upward from an upper surface of platen **2204** for allowing the user to handle or remove platen-sleeve subassembly **2200** from housing **100** of bioreactor **10** (FIG. **1**). Although the quadrilateral shape is shown for sleeve **2202** and platen **2204**, other suitable geometric shapes, such as cylindrical or oval configurations, can be used to suit different applications.

(50) In the illustrated embodiment, platen **2204** can be coated with an adhesive interface, such as collagen, tissue adhesive, gelatin, or other similar materials, applied to an upward-facing surface of platen **2204**. The adhesive interface promotes cell adhesion of tissue construct **101** to platen **2204** within platen-sleeve subassembly **2200**. Sleeve **2202** can be temporarily sealed spheroid-tight either by friction fit or with biocompatible adhesive to platen **2204**, thereby making platen-sleeve subassembly **2200**. However, nutrients can still pass through a junction **2214** between sleeve **2202** and platen **2204**.
(51) Referring now to FIGS. **23-24**, in various embodiments, sleeve **2202** and/or platen **2204** are configured to support tissue construct **101** such that perfusion opening(s) **2207** of platen **2204** align with at least one of perfusion channel(s) **2216** in tissue construct **101**. Thus, the nutrients can pass through perfusion openings(s) **2207** and perfusion channel(s) **2216** as illustrated in arrows **2218**.
(52) Referring now to FIGS. **25-26**, in various embodiments, platen-sleeve subassembly **2200** can be placed into a cavity **2500** formed on a top surface of a cast mold **2502** having a substantially cylindrical body. Cavity **2500** includes one or more tines or needles (e.g., poles or stumps) **2504** extending upward from an inner bottom surface of cavity **2500** such that each needle **2504** corresponds with at least one perfusion opening **2207** of platen **2204** and at least one perfusion channel **2216** of tissue construct **101**.
(53) For example, platen-sleeve subassembly **2200** can be inserted into cavity **2500** of cast mold **2502** over needles **2504** of cast mold **2502** such that needles **2504** penetrate corresponding perfusion opening(s) **2207** of platen **2204** and perfusion channel(s) **2216** of tissue construct **101**. Then, cellular spheroids or other biological material and medium are poured into cavity **2500** of cast mold **2502**. In embodiments, the medium can also be in the space within cast mold **2502** surrounding platen-sleeve subassembly **2200**. As such, the biological material is allowed to mature. For example, in a spheroid case, the spheroids are allowed to fuse into tissue construct **101** providing simultaneous molding and platen adhesion. In embodiments, cast mold **2502** includes one or more handling extensions **2506** extending upward from an upper surface of cast mold **2502** for easy handling.
(54) Referring now to FIG. **27**, after a predetermined fusion period, platen-sleeve subassembly **2200** having tissue construct **101** can be removed from cast mold **2502**. Tissue construct **101** is held to platen **2204** through adhesion or other means (e.g., sleeve **2202**). When tissue construct **101** is removed, a mold design including perfusion channel(s) **2216** of tissue construct **101** is created (e.g., microchannels). Notably, tissue construct **101** has a self-supporting feature where tissue construct **101** having the microchannels can withstand its own weight without or independent of any supporting structures. For example, the self-supporting features are created by cells in tissue construct **101** and an extracellular matrix the cells secrete during the fusion period. Sleeve **2202** is designed to contain the spheroids during fusion but sleeve **2202** can be treated to prevent cell adhesion so the resulting tissue is not supported by sleeve **2202** but by its own cells and the extracellular matrix. Further, in a bioink case, the resulting tissue can also be self-supporting when the tissues are perfused with platen-aligned microchannels and the self-supporting feature without any separate support structure. Depending on a shape of sleeve **2202**, tissue construct **101** can be any geometric shape, such as cylindrical or square column shapes. Although one platen **2204** is shown for illustration purposes, any number of platens can be used to suit different applications. Suitable arrangements of platens **2204** are contemplated, e.g., a top-bottom configuration and a side-to-side configuration.
(55) Referring now to FIG. **28**, a perfusion module **2800** can be used with platen-sleeve subassembly **2200** and has a quadrilateral column body. For example, perfusion module **2800** can be inserted into perfusion chamber **105** of bioreactor **10**. Platen-sleeve subassembly **2200** having tissues is placed onto perfusion module **2800**. Perfusion module **2800** has a rectangular shape when viewed from above and includes four sides **2802**, a top side **2804**, and a bottom side **2806**. In FIG. **28**, platen-sleeve subassembly **2200** can be placed into an indent **2808** formed on top side **2804** of

perfusion module **2800**. The tissues can be perfused with sleeve **2202** in place (without removing sleeve **2202**), if desired. In some embodiments, however, sleeve **2202** is removed to leave tissue construct **101** for tissue perfusion such that the fluid can travel through tissue construct **101**, platen **2204**, and perfusion channel(s) **2216** of tissue construct **101** unimpeded in a predetermined flow path, thereby allowing the tissue perfusion. As with cast mold **2502**, perfusion module **2800** also includes one or more handling extensions **2810** extending upward from top side **2804** of perfusion module **2800** for easy handling. A holder **2812** can be used to securely hold platen-sleeve subassembly **2200** having tissue construct **101** in indent **2808** of perfusion module **2800**.

(56) Referring now to FIG. **29**, an illustrative method **2900** for biofabricating a scaffold-free tissue is shown. It will be described with reference to FIGS. **1-28**. However, any suitable structure can be employed. Although sub-blocks **2902-2916** are illustrated, other suitable sub-blocks can be employed to suit different applications. It should be understood that the blocks within the method can be modified and executed in a different order or sequence without altering the principles of the present disclosure.

(57) At block **2902**, a user or a robotic system (not shown) positions platen-sleeve subassembly **2200** within cavity **2500** of cast mold **2502** such that needles **2504** of cast mold **2502** are inserted into corresponding perfusion opening(s) **2207** of platen **2204**.

(58) At block **2904**, cellular spheroids can be placed into platen-sleeve subassembly **2200** such that the spheroids contact with a floor or surface of platen **2204** to be adhered to or otherwise secured to the floor. Platen-sleeve subassembly **2200** can be temporarily or removably coupled to cast mold **2502**.

(59) At block **2906**, platen-sleeve subassembly **2200** can be filled with a fluid. For example, the fluid can provide a passage of nutrients and media using an interface, such as junction **2214**, between platen **2204** and walls of the platen (e.g., sleeve **2202**).

(60) At block **2908**, the spheroids are fused with platen **2204** after a predetermined fusion period.

(61) At block **2910**, platen-sleeve assembly **2200** is removed from cast mold **2502** after the predetermined fusion period and placed onto perfusion module **2800**.

(62) At block **2912**, perfusion module **2800** is placed in perfusion chamber **105** of bioreactor **10**, e.g., using the robotic system.

(63) At block **2914**, a negative volume is created when cast mold **2502** is removed to generate channels in the resulting biofabricated tissue (e.g., tissue construct **101**). The channels are intrinsically aligned with perfusion opening(s) **2207** in platen **2204** such that the fluid can be perfused through platen **2204** and tissue construct **101**.

(64) At block **2916**, a self-supporting tissue is generated, using tissue construct **101**, which is adhered to platen **2204** having perfusion opening(s) **2207** aligned with perfusion channel(s) **2216** in tissue construct **101** without using intervening non-tissue materials penetrating through tissue construct **101**. Any of the blocks **2902-2916** can be repeated as desired.

(65) While this disclosure has been described as having an exemplary design, the present disclosure may be further modified within the spirit and scope of this disclosure. This application is therefore intended to cover any variations, uses, or adaptations of the disclosure using its general principles. Further, this application is intended to cover such departures from the present disclosure as come within known or customary practice in the art to which this disclosure pertains.

(66) Furthermore, the scope is accordingly to be limited by nothing other than the appended claims, in which reference to an element in the singular is not intended to mean “one and only one” unless explicitly so stated, but rather “one or more.” Moreover, where a phrase similar to “at least one of A, B, or C” is used in the claims, it is intended that the phrase be interpreted to mean that A alone may be present in an embodiment, B alone may be present in an embodiment, C alone may be present in an embodiment, or that any combination of the elements A, B or C may be present in a single embodiment; for example, A and B, A and C, B and C, or A and B and C.

(67) In the detailed description herein, references to “one embodiment,” “an embodiment,” “an

example embodiment," etc., indicate that the embodiment described may include a particular feature, structure, or characteristic, but every embodiment may not necessarily include the particular feature, structure, or characteristic. Moreover, such phrases are not necessarily referring to the same embodiment. Further, when a particular feature, structure, or characteristic is described in connection with an embodiment, it is submitted that it is within the knowledge of one skilled in the art with the benefit of the present disclosure to affect such feature, structure, or characteristic in connection with other embodiments whether or not explicitly described. After reading the description, it will be apparent to one skilled in the relevant art(s) how to implement the disclosure in alternative embodiments.
(68) Furthermore, no element, component, or method step in the present disclosure is intended to be dedicated to the public regardless of whether the element, component, or method step is explicitly recited in the claims. No claim element herein is to be construed under the provisions of 35 U.S.C. 112(f) unless the element is expressly recited using the phrase "means for." As used herein, the terms "comprises," "comprising," or any other variation thereof, are intended to cover a non-exclusive inclusion, such that a process, method, article, or apparatus that comprises a list of elements does not include only those elements but may include other elements not expressly listed or inherent to such process, method, article, or apparatus.

Claims

1. A bioreactor for flowing a liquid medium through one or more through channels in a tissue construct, the bioreactor comprising: a housing that defines a single interior chamber in the bioreactor, the interior chamber having a floor, side walls and a cover, where the interior chamber receives the liquid medium and the tissue construct to be cultured; a tissue construct holder in the interior chamber, the tissue construct holder comprising: a base on the interior chamber floor, the base having a bottom surface, a top surface, and an opening extending completely through the base, and, a first platen having a bottom surface, a top surface, and an opening extending completely through the first platen, where the first platen is removably secured to the base and the bottom surface of the first platen abuts the top surface of the base and where the opening in the base and the opening in the first platen align and are also alignable with the one or more through channels of the tissue construct; a second platen having a bottom surface, a top surface, and an opening extending completely through the second platen, where the top surface of the second platen is configured to securely hold the channeled tissue construct, where the second platen is removably secured to the first platen and the bottom surface of the second platen abuts the top surface of the first platen and where the opening in the base, the opening in the first platen, and the opening in the second platen align and are also all alignable with the one or more through channels of the tissue construct; wherein the openings align along a common vertical axis; wherein the top surface of the first platen and the bottom surface of the second platen are planar; a first port coupled to an outside of the housing; a second port coupled to the outside of the housing;a first liquid medium flow channel in the housing that extends from the first port through the chamber floor and communicates with the opening in the bottom surface of the base of the tissue construct holder such that a first liquid medium flow path exists between the first liquid medium flow channel, the opening in the base, the opening in the first platen, an opening in the second platen, and the one or more through channels of the tissue construct; and, a second liquid medium flow channel in the housing that extends from the second port through the chamber housing to an opening in the interior chamber such that a second liquid medium flow path exists between the second liquid medium flow channel and the interior chamber opening.
2. The bioreactor of claim 1, where the first port coupled to the outside of the housing is an inlet port and the second port coupled to the outside of the housing is an outlet port.
3. The bioreactor of claim 1, where the first port coupled to the outside of the housing is an outlet

port and the second port coupled to the outside of the housing is an inlet port.
4. The bioreactor of claim 1, further comprising a third port coupled to the outside of the housing.
5. The bioreactor of claim 1, where the bioreactor comprises a 3D printed material.
6. The bioreactor of claim 1, where the base of the tissue construct holder includes two separate extensions extending upwards from the top surface of the base to receive and to securely hold the first platen.
7. The bioreactor of claim 1, further comprising an observing/analyzing port.
8. The bioreactor of claim 1, where the cover is coupled with the housing and seals the chamber.
9. The bioreactor of claim 1, where the cover comprises an observing/analyzing portion.
10. The bioreactor of claim 1, where the first platen includes at least one extension extending upwards from the top surface of the first platen.
11. The bioreactor of claim 1, where the first platen further comprises at least one channel-creating element projecting upward from the top surface of the first platen.
12. The bioreactor of claim 1, where the first platen further comprises at least one channel-creating element projecting upward from the top surface of the first platen and where the at least one channel-creating element of the first platen is selected from the group consisting of a tine, a needle, a pole and a stump.
13. The bioreactor of claim 1, where the top surface of the first platen is configured to securely hold the channeled tissue construct and where the top surface of the first platen comprises an adhesive coating.
14. The bioreactor of claim 1, where the top surface of the first platen is configured to securely hold the channeled tissue construct and where the top surface of the first platen is free of an adhesive coating.
15. The bioreactor of claim 1, where the first platen further comprises a sleeve.
16. The bioreactor of claim 1, where the first platen further comprises a sleeve and the sleeve is temporarily sealable to the platen.
17. The bioreactor of claim 1, where the first platen further comprises a sleeve and where the sleeve further comprises at least one extension extending upward from a top surface of the sleeve.
18. The bioreactor of claim 1, where the first platen further comprises a sleeve and where a junction is disposed between the sleeve and the first platen.
19. The bioreactor of claim 1, where the sleeve comprises a treatment to prevent cell adhesion.
20. A bioreactor for flowing a liquid medium through and inside at least one channel in a tissue construct, the bioreactor consisting of: a housing that defines a single interior chamber in the bioreactor, the interior chamber having a floor, side walls and a cover, where the interior chamber receives the liquid medium and the channeled tissue construct to be cultured; a tissue construct holder in the interior chamber, the tissue construct holder having: a base on the interior chamber floor, the base having a bottom surface, a top surface, and an opening extending completely through the base, and, a first platen having a bottom surface, a top surface, and an opening extending completely through the first platen, where the first platen is removably secured to the base and the bottom surface of the first platen abuts the top surface of the base and where the opening in the base and the opening in the first platen align and are also alignable with the through channel of the tissue construct; a first port coupled to an outside of the housing; a second port coupled to the outside of the housing; a first liquid medium flow channel in the housing that extends from the first port though the chamber floor and communicates with the opening in the bottom surface of the base of the tissue construct holder such that a first liquid medium flow path exists between the first liquid medium flow channel, the opening in the base, the opening in the platen and the through channels of the tissue construct; and, a second liquid medium flow channel in the housing that extends from the second port through the chamber housing to an opening in the interior chamber such that a second liquid medium flow path exists between the second liquid medium flow channel and the interior chamber opening.

21. A bioreactor for flowing a liquid medium through one or more through channels in a tissue construct, the bioreactor comprising: a housing that defines a single interior chamber that receives the liquid medium and the tissue construct to be cultured in the bioreactor; a tissue construct holder in the interior chamber comprising: a base having a top surface and an opening extending completely through the base, a first platen having a bottom surface, a top surface, and an opening extending completely through the first platen, where the first platen is removably secured to the base and the bottom surface of the first platen abuts the top surface of the base and where the opening in the base and the opening in the first platen align and are also alignable with the one or more through channels of the tissue construct; and a second platen having a bottom surface, a top surface, and an opening extending completely through the second platen, where the top surface of the second platen is configured to securely hold the channeled tissue construct, where the second platen is removably secured to the first platen and the bottom surface of the second platen abuts the top surface of the first platen and where the opening in the base, the opening in the first platen, and the opening in the second platen align and are also all alignable with the one or more through channels of the tissue construct; wherein the top surface of the first platen and the bottom surface of the second platen are planar, and wherein the openings align along a common vertical axis.