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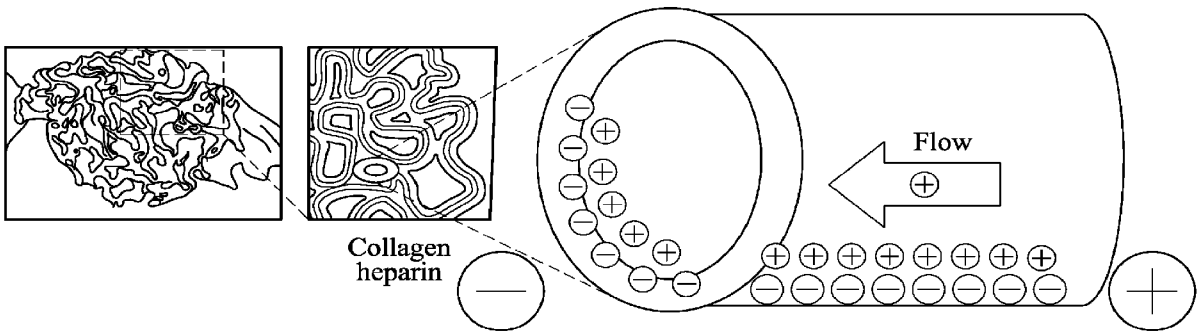

FIG. 5

(57) **Abstract:** The present embodiments relate to devices and methods for treatment of edema. In some embodiments devices and methods are described using electric stimulation applied along implanted scaffolds to enhance lymphatic regeneration and repair. A device may be comprised of a biocompatible implant for a transfer of an extracellular fluid from one part of a mammal body to other part of the mammal body, the biocompatible implant may include a membrane having at least one capillary channel, where the at least one capillary channel has a positively or negatively charged internal surface.

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DEVICES AND METHODS FOR EDEMA TREATMENT

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of, and priority to, U.S. Provisional Application No. 63/458,355, filed on April 10, 2023, which is hereby incorporated by reference in its entirety.

TECHNICAL FIELD

[0002] The present disclosure related generally to devices and methods for treatment of edema. More specifically, the present disclosure relates to devices and methods using electric stimulation applied along implanted scaffolds to enhance lymphatic regeneration and repair.

BACKGROUND

Background on electrical stimulation for edema treatment.

[0003] Electric stimulation (ES), or application of electric field as a means to reduce tissue edema, has been explored as therapeutic approach clinically [9] and experimentally [10]. In a simplified lymphedema model, Cook et al [11] demonstrated the capability of ES to increase lymphatic uptake of interstitial flow. In addition to enhancing the flow, ES stimulates molecular and cellular processes including secretion of trophic factors, enhancement of wound healing, stimulation of lymphangiogenesis and reduction of fibrosis, which benefit resolution of lymphedema [12]. Treatment with low-intensity and extremely low frequency electric fields, supplementary to manual lymphatic drainage, can significantly enhance pain alleviation and swelling reduction in patients with secondary lymphedema compared with manual lymphatic drainage alone [13], though a similar treatment in another

study only demonstrated significant reduction in pain, heaviness and tightness, in contrast to manual lymphatic drainage which showed no significant changes in any of the outcomes [14]. Perhaps, the differences in the outcomes correspond to the different regimens of ES applied. In patients with lymphedema, application of transcutaneous electrical nerve stimulation was confirmed to be effective in reducing edema and pain [15]. A pilot study in healthy subjects has demonstrated that a wearable ES device is capable to increase a lymphatic function [16].

[0004] Recently, ES in the form of continuous application of microcurrent by implanted device has been demonstrated to reduce tissue edema of cardiac muscle and improve heart function in patients with heart failure [17]. The authors further suggested that edema reduction was triggered by electro-osmosis [18], which describes the phenomenon of the fluid movement through a capillary vessel bearing a surface charge under an electrical field applied alone to the vessel [19-21]. Electro-osmotic flow may occur through small-channel structures such as gap junctions, capillaries, cells, cell membranes, and across a heterogenous tissue. In addition to the flow generated by pulsatile or osmotic and hydrostatic pressure differences, electrokinetic flow is a relevant transport mechanism in even the smallest lymphatic and blood vessels [22]. In the context of myocardium, edema formation is viewed in part as a disturbed electrical environment generating a potential gradient. This environment includes the negatively charged intraluminal layer (glycocalyx) which controls the permeability of the capillary wall and, in turn, the fluid balance and pressure conditions in the interstitium [23-25]. An externally applied weak electric current together with an electrical field normalizes the electrical environment, which results in increasing lymphatic flow by supporting the electrokinetically induced transport of electro-osmosis and electrophoresis and may also influence the charge of the glycocalyx [26]. This view is in line with earlier studies of ES effect on interstitial flow and edema reduction, where the authors

proposed that low electrical current displaces the negatively charged plasma proteins found in the interstitium of the traumatized areas [27]. They hypothesized that this increased mobility should accelerate protein uptake by the lymphatic capillaries, which facilitates lymphatic flow, as an established mechanism for extracellular fluid uptake. Further, an effective displacement of the proteins into the lymphatic capillaries may depend on the stimulus waveform or the total amount of current passed through the interstitial spaces, and the unidirectional current flow is desired for edema reduction, through direct nonexcitatory effects on charged particles at the cellular level [28].

[0005] The notion that interstitial flow can be enhanced through electroosmotic mechanism has been supported by recent in-vitro study, in which the authors demonstrated electrokinetically-driven perfusion of cell-loaded microporous matrix with negatively charged surface [29].

[0006] Unlike in ischemic myocardium, where the vasculature (blood and lymphatic) remains in place, in the case of the secondary lymphedema, after lymph node removal the wound area is largely devoid of functional lymphatics. This lack of lymphatics means that the accumulated interstitial fluid has to find a way to drain out of the area for edema to be resolved. Anatomically, lymphatic system is arranged in lymphosomes, each of them drains or collects the lymph from a specific body area/part [30], with no or minimum flow occurring across the borders of lymphosome. Removal of major lymph nodes in one lymphosome may induce spontaneous rerouting of regenerated lymphatics toward an adjacent lymphosome [31,32]. These findings provided the ground for the treatment approach when the implanted scaffolds enhance the routes of a spontaneous regeneration [32].

Background on biocompatible scaffolds for edema treatment.

[0007] BioBridge™ Collagen Matrix, developed by Fibralign Corp [32-34] has an open structure composed of aligned collagen fibrils which allows the cells to attach throughout the scaffold and guides their migration along the fibrils. BioBridge (see Figure 1) mimics the nanotopography of the native extracellular matrix and determines the organization of the cells (e.g. alignment) and their phenotype, promoting new vessel formation. This device bridges the gaps between the existing lymphatics. The concept of an artificial conduit to drain lymphatic fluid through capillary action was introduced previously using silk sutures [42], Teflon multifilament material [43], and silicone tubing [44]. These studies validate the concept of creating an artificial channel for the acute relief from lymphedema.

[0008] The idea of implantable device made of a silicone catheter connected to an active pump has been tested in the lymphedema rat model to drain lymphatic fluid from affected hindlimb lymphosome to unaffected healthy ipsilateral lymphosome [45]. This device used a conventional electric pump to transfer the interstitial fluid. There is an important distinction between BioBridge and all other scaffold mentioned above, - BioBridge is the only fully biodegradable scaffold which provides temporary channels for lymphatic drainage and induces a formation of a new lymphatics [32-34]. It is safely resorbed after fulfilment of its function.

[0009] While developments have been made, further work and innovation is necessary to provide enhanced treatments for edema and repair of the lymphatic system.

SUMMARY

[0010] Embodiments of the present disclosure provide a novel treatment where electric stimulation (ES) is applied along implanted scaffolds which further enhances lymphatic regeneration and repair. In some embodiments, methods are provided comprising: (1)

bridging an area of lymphatic obstruction with implanted thread-like scaffolds providing microcapillary channels between the healthy lymph draining areas or between the impaired lymphatic drainage area and healthy area in adjacent lymphosome and (2) enhancing the drainage of accumulated interstitial fluid or CSF electrokinetically by applied low current alone the microcapillary channels.

[0011] In another aspect, a biocompatible implant is provided for a transfer of an extracellular fluid from one part of a mammal body to other part of the mammal body, the biocompatible implant comprising: a membrane having at least one capillary channel, where the at least one capillary channel has a positively or negatively charged internal surface. In other embodiments, a biocompatible implant is provided for transfer of an extracellular fluid from one part of a mammal body to other part of the mammal body comprising: at least one capillary channel, and wherein a first end of the capillary channel is placed into one part of the mammal body and a second end of the capillary channel is placed into other part of the mammal body wherein the channel induces a flow of the extracellular fluid to transfer the extracellular fluid from one part of a mammal body to other part of the mammal body.

[0012] Additionally, embodiments of the present disclosure further provide a system for transferring an extracellular fluid from one part of a mammal body to other part of the mammal body, the system comprising: a biocompatible implant as described above; and an electric field generator configured to generate an electric field along the biocompatible implant.

BREIF DESCRIPTION OF THE DRAWINGS

[0013] Embodiments of the present invention are illustrated by way of example and not limitation in the figures of the accompanying drawings, in which like references indicate similar elements and in which:

[0014] FIGs. 1A – 1E are photographs illustrating examples of implantable and biodegradable scaffolds with multi-lumen microchannels that enable a capillary flow of extracellular fluid or CSF, according to some embodiments of the present disclosure;

[0015] FIGs. 2A – 2C are photographs illustrating examples of implantable and biodegradable scaffolds with multi-lumen microchannels that enable a capillary flow of extracellular fluid or CSF, according to some embodiments of the present disclosure;

[0016] FIGs. 3A – 3B are photograph showing a folded membrane which may be used to form the scaffolds, according to some embodiments of the present disclosure;

[0017] FIG. 4 is a photograph showing capillary flow induced by the scaffolds according to the present disclosure;

[0018] FIG. 5 is a schematic diagram showing a scaffold with negatively charged coating according to embodiments of the present disclosure;

[0019] FIG. 6 presents a simple experiment demonstrated electro-osmotic flow through the multilumen fibrillar collagen scaffold (BioBridge) with the modified surface with zeta potential 20 mV.

[0020] FIGs. 7A – 7B are schematic diagrams illustrating treatment methods with implanted scaffolds according to embodiments of the present disclosure;

[0021] FIG. 8A – 8B are a schematic diagram illustrating electro-osmotic flow generation in a rat lymphedema model to transfer the interstitial fluid from the edema area to a health lymphosome;

[0022] FIG. 9 and FIG. 10 are schematic representations of a biocompatible scaffold implanted to connect the dura layer and/or meningeal lymphatics with the superficial lymphatic system, and showing that the flow can be enhanced by electro-osmotic pumping, with placing one electrode in the dura layer and a second electrode under the head skin, according to embodiments of the present disclosure;

[0023] FIG. 11 is a schematic diagram presenting an alternative approach to direct CSF flow from meningeal lymphatics to the superficial cervical lymph node.

[0024] FIG. 12 is a cross-sectional view of a biocompatible implant according to embodiments of the present disclosure, which may be utilized in-vitro or in-vivo for nanotransfection.

DETAILED DESCRIPTION

[0025] The following terms are used herein: Edema is a condition characterized by an excess of watery fluid collecting in the cavities or tissues of the body. As an example, lymphedema is a common complication in cancer survivors, as well as patients who undergo pelvic dissections or radiation therapy, such as treatment for breast cancer and other cancers. Other types of edemas include, but are not limited to, postoperative edema, myocardial edema, or wound edema. Some neurological disorders are also characterized by an abnormal accumulation of cerebrospinal fluid (CSF) within the brain or reduced drainage of CSF to the lymphatic system. Electroosmotic flow is the motion of liquid induced by an applied potential across a porous material, or capillary channel, or membrane, or microchannel, or any other fluid holding scaffold. Lymphosome is a particular region of the body where lymphatic vessels connect to the same subgroup of regional lymph nodes.

[0026] The inventor has discovered a novel treatment where electric stimulation (ES) is applied along implanted scaffolds which further enhances lymphatic regeneration and repair. As described in detail herein and with reference to the figures, the inventive approach includes (see Fig. 7 or Fig. 9): (1) bridging an area of lymphatic obstruction with implanted thread-like scaffolds providing microcapillary channels between the healthy lymph draining areas or between the impaired lymphatic drainage area and healthy area in adjacent

lymphosome and (2) enhancing the drainage of accumulated interstitial fluid or CSF electrokinetically by applied low current alone the microcapillary channels.

[0027] As described herein, edema can be treated, at least in part, using a scaffold with capillary channels facilitating a flow of extracellular fluid or CSF away from the cavities or tissues. Figures 1 and 2 illustrates examples of the implantable and biodegradable scaffolds with multi-lumen microchannels that enable a capillary flow of extracellular fluid or CSF. In at least some embodiments, the scaffolds are made by a folded membrane like one that presented, for example, in Figure 3. In at least some embodiments, the fibrils/fibers are aligned in a same direction as the direction of the microchannels, see, for example, the scaffold presented in the Figure 1.

[0028] The scaffolds can be made of any suitable, biocompatible material including, but not limited to, collagen, fibronectin, fibrin, laminin, elastin, hyaluronic acid, chitosan, silk, silicone, peptides, biodegradable block copolymers, lactide and glycolide polymers, caprolactone polymers, hydroxybutyric acids, polyanhydrides and polyesters, polyphosphazenes, polyphosphoesters, poly(ethylene glycol) (PEG), poly(ethylene oxide) (PEO), PEG or PEO with different end-functionalities and, optionally, bifunctional cross-linkers and crosslinking agents, or the like or any combination thereof.

[0029] Figure 4 illustrates one example in which a scaffold made by a folded collagen membrane was vertically dipped into an aqueous solution of methylene blue (0.1% w/v). The capillarity of the scaffold caused the solution to rise along the membrane. The capillary flow rates were variable between the samples of the scaffolds ranging from 0.5cm/min to 2.2cm/min. No difference was observed in an incubation chamber with variable relative humidity.

[0030] To enhance flow of fluid along the capillary channels, the surface of the capillary channels or any other suitable portion of a scaffold surface can be charged or modified such

that the resulting surface forms an electric double layer in the fluid. Applying a potential across such capillary channels or the scaffold can result in electroosmotic flow of fluid (see, for example, Figure 5) along the capillary channels or through the scaffold (such as, for example, a porous material, capillary tube, membrane, microchannel, or any other fluid holding conduit.) This electroosmotic flow can be used to remove fluid from cavities or tissues of the body to treat an edema.

[0031] In at least some embodiments, the electric charge is constrained to a two-dimensional surface, such as, for example, along the interior surface of capillary channels. The surface charge density can be measured in coulombs per square meter (C•m−2) to describe the charge distribution on the surface.

[0032] In at least some embodiments, the membrane or capillary channel has a positively charged internal surface. In at least some embodiments, the membrane or capillary channel has a negatively charged internal surface.

[0033] As an example, the membrane or capillary channels can be treated with heparin to produce a negatively charged internal surface. Heparin is a glycosaminoglycan with a relatively high negative charge density due to abundant sulfate groups. In at least some embodiments, heparin binds to various proteins and growth factors via electrostatic interactions. Heparin may also bind to specific heparin-binding sites. Immobilization of heparin on collagen matrices produces a material which has been used to stimulate endothelial cell proliferation. In at least some embodiments, the negatively charged surface can form a diffuse double layer with counterions present in the tissue fluid, and when placed under electric field, stimulate the flow of fluid across/through the membrane or capillary channels.

[0034] Any other suitable, biocompatible surface modification can be applied to the membrane or capillary channels to provide a positively or negatively charged surface. Such surface modification can include, but is not limited to, binding charged or chargeable

molecules or substituents to the surface, adding charged or chargeable substituents to the surface, radicalizing the surface, remove some charged or chargeable substituents of the surface, or the like or any combination thereof.

[0035] For example, the native amino groups and carboxylic acid groups of collagen can be modified to change the ratio of positive and negative charges on the collagen fibrils at a given pH. It is also possible to remove the native amino groups of collagen by treatment with nitrous acid using a deamination reaction. In this case the net result will be more negative charges from the native carboxylic groups. This method provides the control of the surface Zeta potential in the range from -5 mV to -20 mV at the neutral pH. The resulting collagen material supports cell viability and proliferation [1].

[0036] To generate electroosmotic flow, an electrical field is applied externally or internally to produce directional flow of interstitial fluid or CSF through the membrane or capillary channels. The direction of the flow depends on the direction of the electric field and the charge (negative or positive) of the surface of the membrane or capillary channels. Any suitable electrical field generator can be used to apply the electrical field.

[0037] As an example, the surface of a collagen scaffold with capillary microchannels or collagen membrane can be modified with heparin to obtain a scaffold with capillary properties and negatively charged surface. The negatively charged scaffold will form a diffuse double layer with counterions present in the tissue fluid, and when placed under electric field, stimulate the flow of fluid across the scaffold. We used the protocol developed earlier [2] for 1:4 heparin to collagen ratio and achieved a range for the ratio as low as 1:20 [3] to adjust the Zeta potential of the collagen surface in the range -10- 20 mV, and based on its response to applied electric field, we achieved reasonable flow rates with lowest voltage. With the aim at the flow rates at least 0.1-2 um/s (physiological range for interstitial flow [4]) and not to exceed 13 um/s (shown to damage the cells [5, 6]) we can use the range of electric fields

between 100 mV/mm and 1000 mV/mm [1], considering that higher voltages (2800 mV/mm for 5 min [7, 8]) may reduce cell viability.

[0038] In at least some embodiments, electrical stimulation can reinforce the treatment of lymphedema progression and complications. In at least some embodiments, the membrane may support lymphangiogenesis in the alignment direction and restore the lymphatic pathways that have been disrupted during the cancer surgery by bridging across damaged lymphatic tissue and providing support needed to effectuate lymphatic repair, and guide and restore the lymphatic function. In at least some embodiments, the application of electric field along the membrane directs the flow of interstitial fluid to regions with healthy lymphatic tissues.

[0039] In at least some embodiments, the membrane is implanted to bridge an area of lymphatic obstruction. In at least some embodiments, a patch lead is placed on the skin near the midline and a coil lead is implanted subcutaneously parallel to the patch lead. In at least some embodiments, electrical stimulation is conducted after the membrane implantation to treat an edema.

[0040] The inventor herein provides a novel treatment when ES applied along the implanted scaffolds further enhances lymphatic regeneration and repair. The proposed approach includes (see Fig. 7 and Fig. 8): (1) bridging an area of lymphatic obstruction with implanted thread-like scaffolds providing microcapillary channels between the healthy lymph draining areas or between the impaired lymphatic drainage area and healthy area in adjacent lymphosome and (2) enhancing the drainage of accumulated interstitial fluid or CSF electrokinetically by applied low current alone the microcapillary channels.

[0041] When applied across the border of impaired lymphatic drainage toward a healthy lymphatics area, the implanted scaffold facilitates the interstitial flow or CSF flow in the direction of healthy lymphatics, reduces fluid accumulation, and enhances lymphatic

regeneration in the affected area. An additional ES helps to enhance the interstitial flow or CSF flow toward the healthy lymphatic bed such that the resulting treatment eliminates lymph accumulation or increases CSF drainage and facilitates lymphatic repair.

[0042] Methods of electric current application - One of the methods of electrical stimulation described in the paragraph 1 above can be used in combination with the thread-like scaffold to induce electrokinetic flow and/or lymphatic repair and regeneration. Specifically, a current can be induced by the electrodes applied to the skin such that at least a part of the scaffold is located between the electrodes (see, Figure 8). Alternatively, the electrodes with or without electrical generator (or battery) can be implanted such that at least a part of the scaffold is located between the electrodes (see, Figure 8). Alternatively, at least one of the electrodes can be inserted into the skin. In particular, the electrodes can generate a DC current or AC current (biphasic or monophasic). Multiple electrodes can be used for the treatment including a belt electrode. A wireless magnetic field stimulation can be used as an alternative.

[0043] An example of connection between meningeal lymphatics and superficial cortical lymphosome is presented in the Figure 9, 10, and 11.

[0044] Electro-osmotic membrane can be also applied for in-vivo or in-vitro nanotransfection. For example, Figure 12 shows a electro-osmotic biocompatible device according to the present disclosure. The biocompatible device may be used in-vitro or in-vivo for nanotransfection. In the exemplary embodiment the device generally includes an electro-osmotic pump coupled with biocompatible scaffold. In an exemplary embodiment (Figure 12) the electrostatic pump (porous layer/membrane sandwiched between conductive layers) may be comprised of a porous glass frit sandwiched between conductive coatings. In some embodiments the conductive layers are comprised of metal nanowires, such as but not

limited to platinum nanowires (PtNWs). The advantage of nanowire coating is high conductivity and preservation of the porous structure of the porous layer/membrane.

[0045] For in-vitro nanotransfection the layer of the membrane with conductive coating is covered by the patterned collagen layer treated with laminin, fibronectin, or other bioactive material to stimulate cell adhesion on the top of the layer. This structure is used as bottom of a cell culture dish and is coupled with the reservoir that may contain any suitable solution, such as for example a plasmid/mRNA solution. An additional electrode can be attached to the top of the culture dish. After the suitable cells are plated on the bottom of the culture dish, an electrical field can be applied between the electrodes to induce nanotransfection through the plated cells and introduce the required plasmids or mRNAs.

[0046] The electrical impulse is generated by an electrical generator (not shown) which is used to apply potential to the top electrode and to the bottom (PtNWs) conductive layer (electroporation).

[0047] The electro-osmotic flow can be initiated by an application of electrical potential between the two coatings sandwiched the porous membrane/layer.

[0048] The electro-osmotic flow can coincide with the electroporation.

[0049] It will be appreciated that the term “present disclosure” as used herein should not be construed to mean that only a single invention having a single essential element or group of elements is presented. Similarly, it will also be appreciated that the term "present disclosure" encompasses a number of separate innovations, which can each be considered separate inventions. Although the present invention has been described in detail with regards to the preferred embodiments and drawings thereof, it should be apparent to those skilled in the art that various adaptations and modifications of embodiments of the invention may be accomplished without departing from the spirit and the scope of the invention. Accordingly, it is to be understood that the detailed description and the accompanying drawings as set forth

hereinabove are not intended to limit the breadth of the invention, which should be inferred only from the following claims and their appropriately construed legal equivalents.

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CLAIMS

I Claim:

1. A method for transfer of an extracellular fluid from a first part of a mammal body to a second part of the mammal body, the method comprising:

implanting a biocompatible scaffold comprising at least one capillary channel having a first end and an opposing second end, wherein the first end of the capillary channel is placed into the first part of the mammal body and the second end of the capillary channel is placed into the second part of the mammal body; and

inducing a flow of the extracellular fluid through the at least one capillary channel to transfer the extracellular fluid from one part of a mammal body to other part of the mammal body.

2. The method of claim 1, wherein the biocompatible scaffold comprising a bundle of the capillary channels.

3. The method of claim 2, wherein the scaffold is a folded membrane.

4. The method of claim 3, wherein the membrane comprises aligned fibrils or fibers.

5. The method of claim 4, wherein a direction of alignment of the aligned fibrils or fibers coincides with a direction of at least one capillary channel.

6. The method of claim 1, wherein at least one capillary channel has a positively charged internal surface.

7. The method of claim 1, wherein at least one capillary channel has a negatively charged internal surface.

8. The method of claim 1, wherein inducing the flow comprises applying an electrical potential across the at least one capillary channel.

9. The method of claim 1, wherein inducing the flow comprises inducing the flow of the extracellular fluid to treat an edema.

10. The method of claim 9, wherein the first part of the mammal body comprises an edema and the second part of the mammal body is a healthy part.

11. The method of claim 10, wherein the healthy part comprises a healthy lymphatic system capable of processing the fluid transferred from the first part of the mammal body.

12. A biocompatible implant for a transfer of an extracellular fluid from one part of a mammal body to other part of the mammal body, the biocompatible implant comprising:

a membrane having at least one capillary channel, where the at least one capillary channel has a positively or negatively charged internal surface.

13. A system for transferring an extracellular fluid from one part of a mammal body to other part of the mammal body, the system comprising:

the biocompatible implant of claim 12; and

an electric field generator configured to generate an electric field along the biocompatible implant.

14. A biocompatible implant for a transfer of an extracellular fluid from one part of a mammal body to other part of the mammal body comprising at least one capillary channel wherein the first end of the capillary channel is placed into one part of the mammal body and the second end of the capillary channel is placed into other part of the mammal body wherein the channel induces a flow of the extracellular fluid to transfer the extracellular fluid from one part of a mammal body to other part of the mammal body.

15. A biocompatible implant according to the claim 14 wherein the biocompatible implant comprising a bundle of capillary channels.

16. A bundle of capillary channels according to the claim 15 wherein the bundle is formed by a folded membrane.

17. A membrane according to the claim 16 wherein the membrane is formed by aligned fibrils or fibers.

18. A membrane according to the claim 16 wherein the membrane is formed by aligned fibrils or fibers and wherein the alignment direction is coincided with the direction of the channel.

19. A biocompatible implant according to the claim 14 wherein the capillary channel has a positively charged internal surface.

20. A biocompatible implant according to the claim 14 wherein the capillary channel has a negatively charged internal surface.

21. A biocompatible implant according to the claim 14 wherein the flow in the channel is induced by an electrical potential applied across the capillary channel.

22. A biocompatible implant according to the claim 15 wherein the first end of the bundle of capillary channels is placed into one part of the mammal body and the second end of the bundle of capillary channels is placed into other part of the mammal body wherein a transport of the extracellular fluid from one part of a mammal body to another part of the mammal body is induced by an electrical potential applied across the bundle of capillary channels.

23. A biocompatible implant according to the claim 14 wherein the flow in the channel is induced by an electrical stimulation applied across the implant.

24. A biocompatible implant for a transfer of an extracellular fluid from one part of a mammal body to other part of the mammal body comprising at least one capillary channel wherein the implant is connected the two parts of the mammal body and transports the extracellular fluid from one part of a mammal body to other part of the mammal body under an influence of an external electrical field applied across the implant which causes an electro-osmotic flow in the capillary channel.

25. A biocompatible implant for a transfer of an extracellular fluid from one part of a mammal body to other part of the mammal body comprising at least one bundle of capillary channels wherein the implant is connected the two parts of the mammal body and transports

the extracellular fluid from one part of a mammal body to other part of the mammal body under an influence of an external electrical field applied across the implant which causes an electro-osmotic flow in the bundle of capillary channels.

26. A biocompatible implant according to the claim 14, 24 or 25 wherein the implant is used to reduce an edema in mammal body including the edema in lymphedema patients, postoperative edema, myocardial edema, wound edema, etc.

27. A biocompatible implant according to the claim 26 wherein the implant is positioned such that one end of the capillary channel or bundle of capillary channels is connected the body part with edema and other part of the capillary channel or bundle of capillary channels is placed into the healthy part of the body where the healthy lymphatic system is capable to process the excessive fluid transferred from the edematous part of the body.

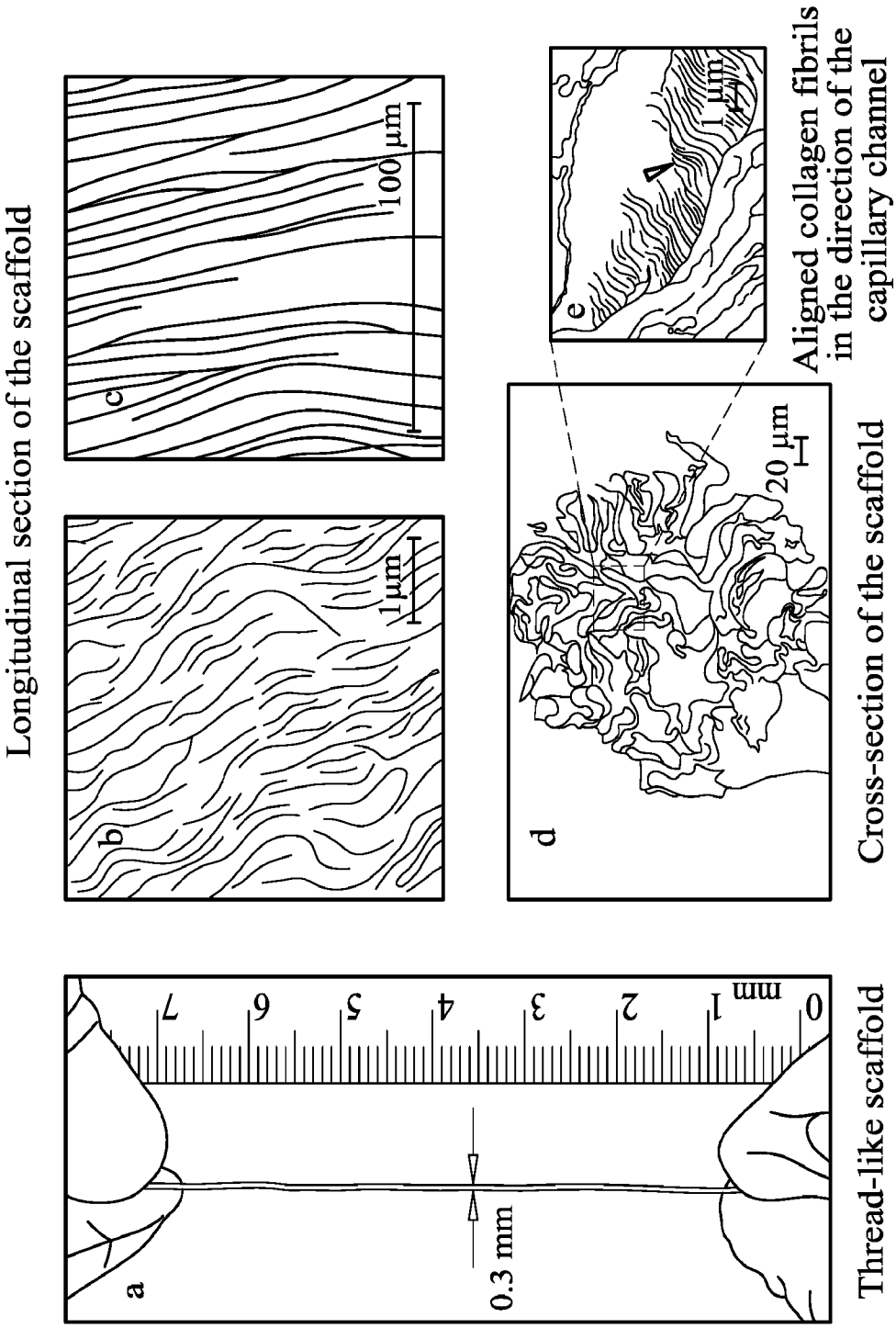

Longitudinal section of the scaffold
Cross-section of the scaffold
Thread-like scaffold
Aligned collagen fibrils in the direction of the capillary channel
a
b
c
d
e
0.3 mm
100 µm
1 µm
20 µm
mm
0
1
2
3
4
5
6
7

FIG. 1

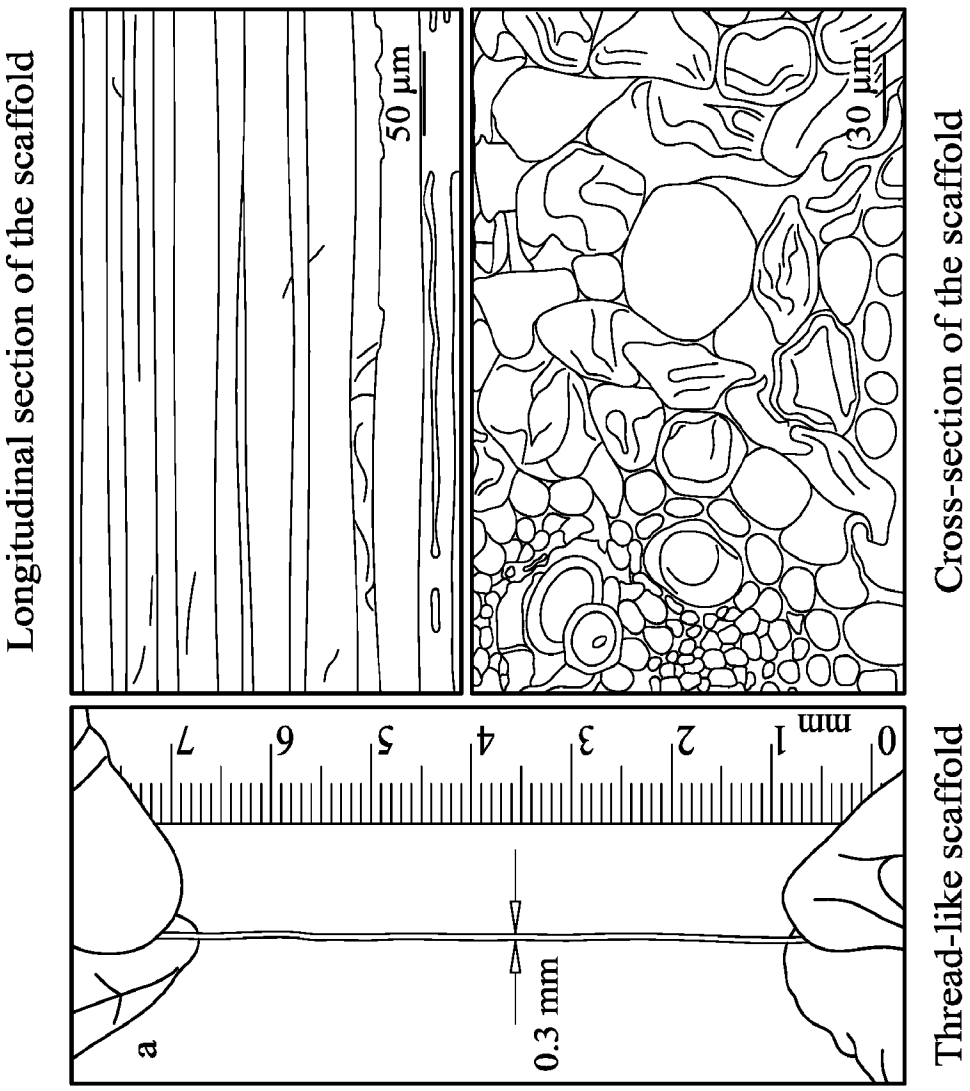
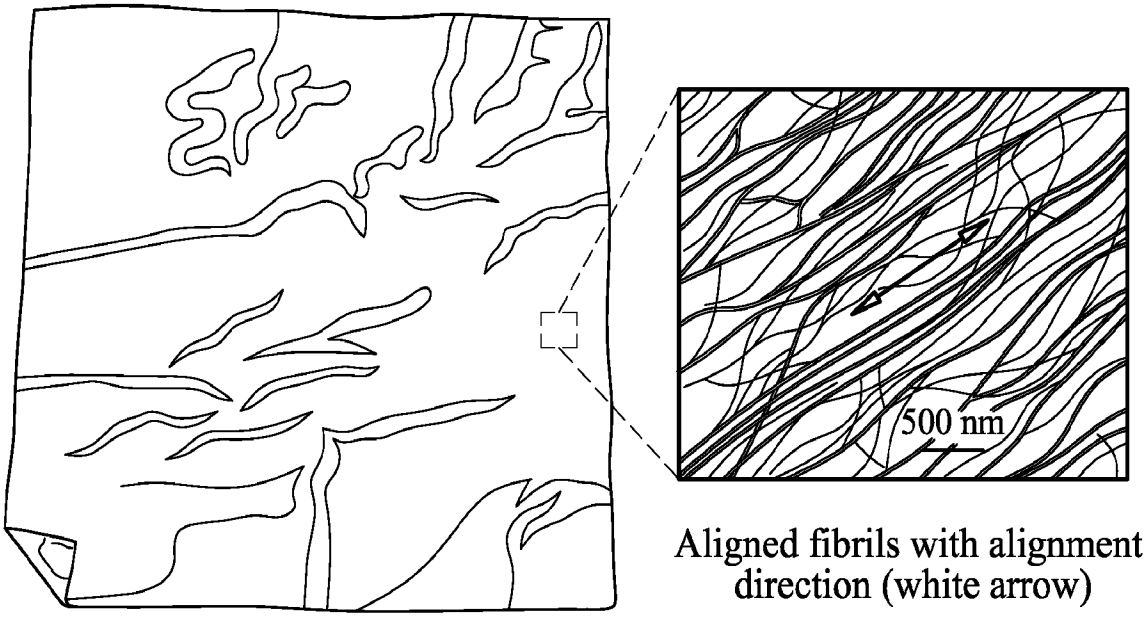

Longitudinal section of the scaffold
50 µm
30 µm
Cross-section of the scaffold
mm
0
1
2
3
4
5
6
7
a
0.3 mm
Thread-like scaffold

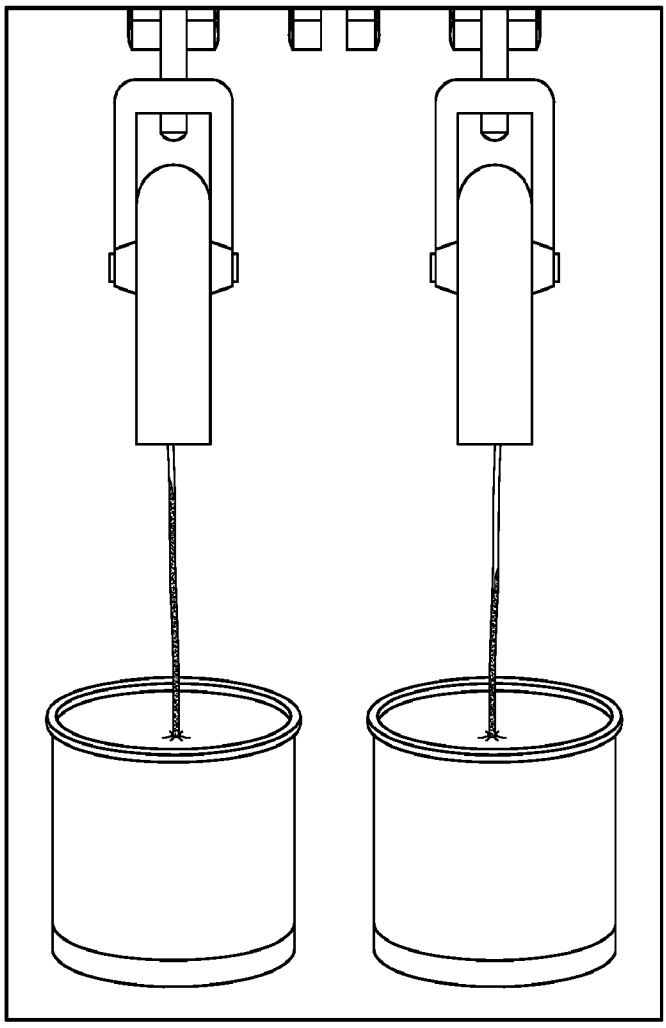
FIG. 2



Membrane formed by aligned fibrils

Aligned fibrils with alignment direction (white arrow)

FIG. 3



Capillary flow induced by the scaffold

FIG. 4

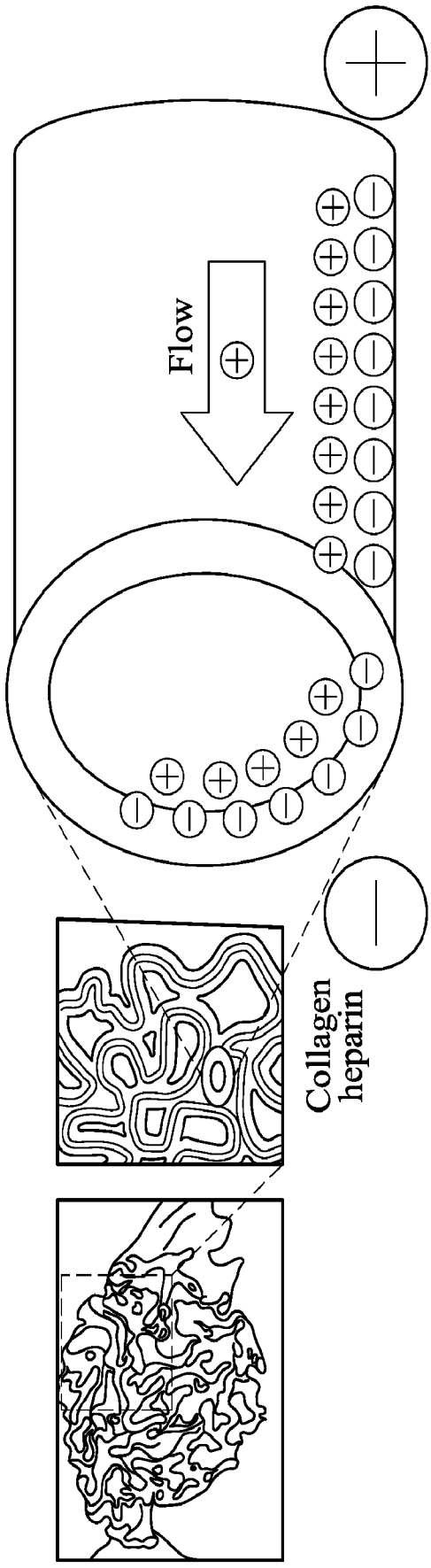


FIG. 5

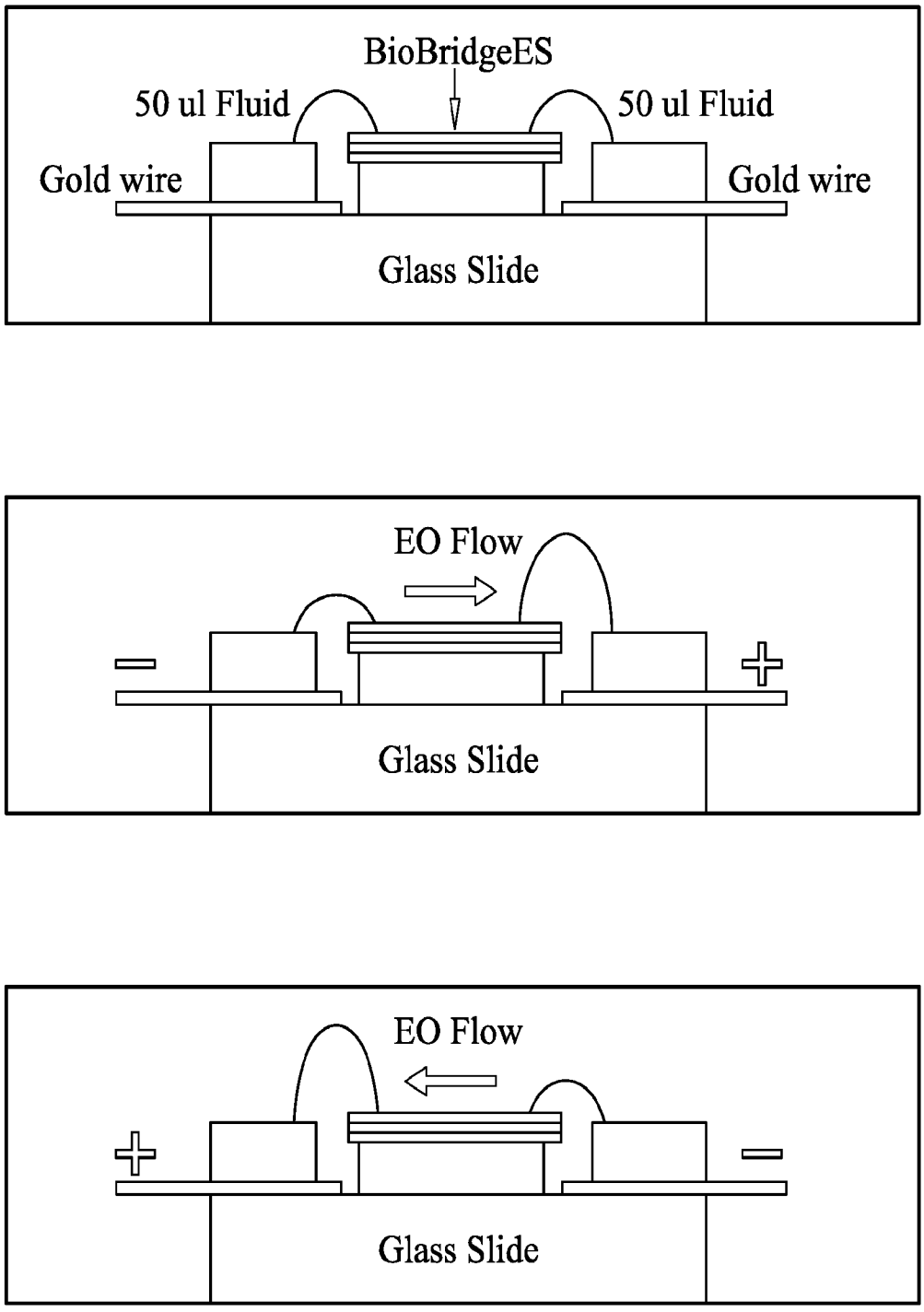

BioBridgeES
50 ul Fluid
50 ul Fluid
Gold wire
Gold wire
Glass Slide
EO Flow
Glass Slide
EO Flow
Glass Slide

FIG. 6

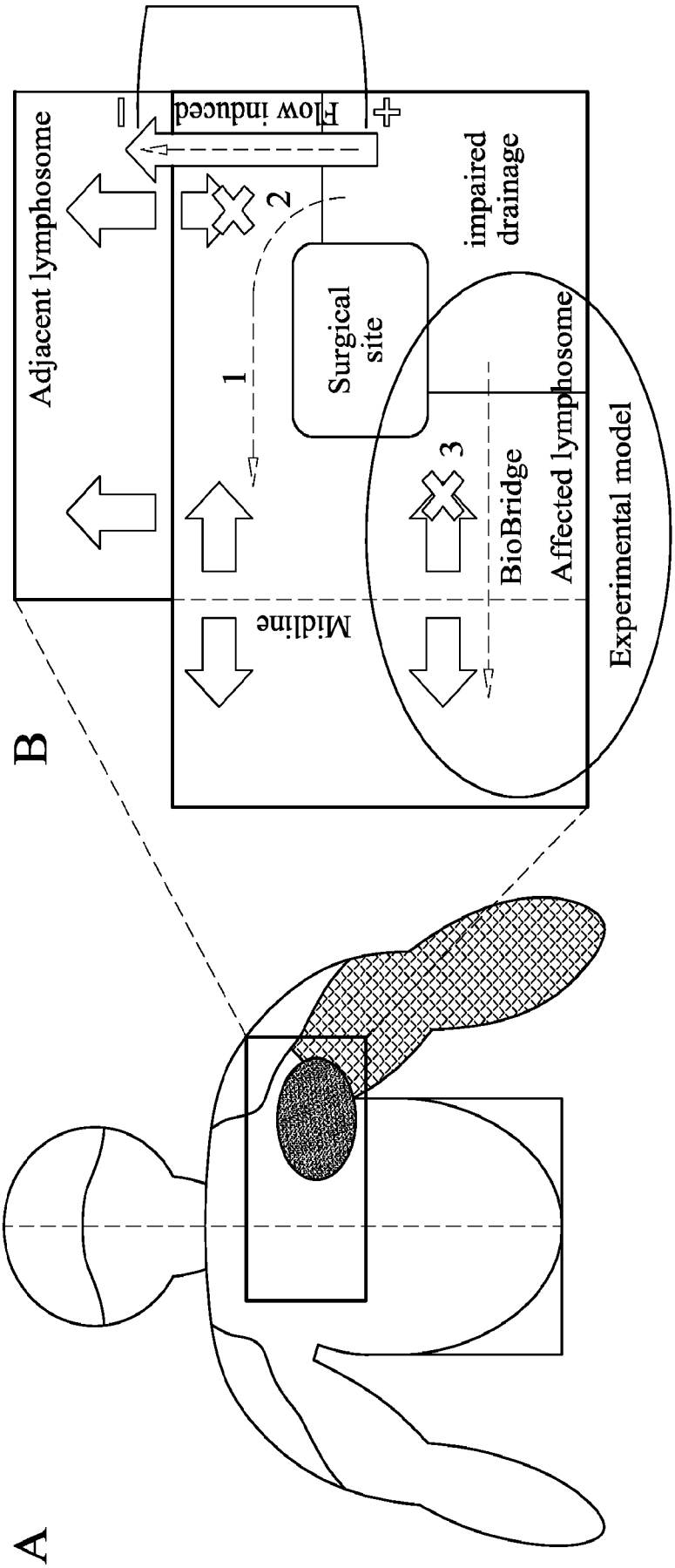

A
B
Flow induced
Adjacent lymphosome
impaired drainage
Surgical site
BioBridge
Affected lymphosome
Experimental model
Midline
1
2
3

FIG. 7

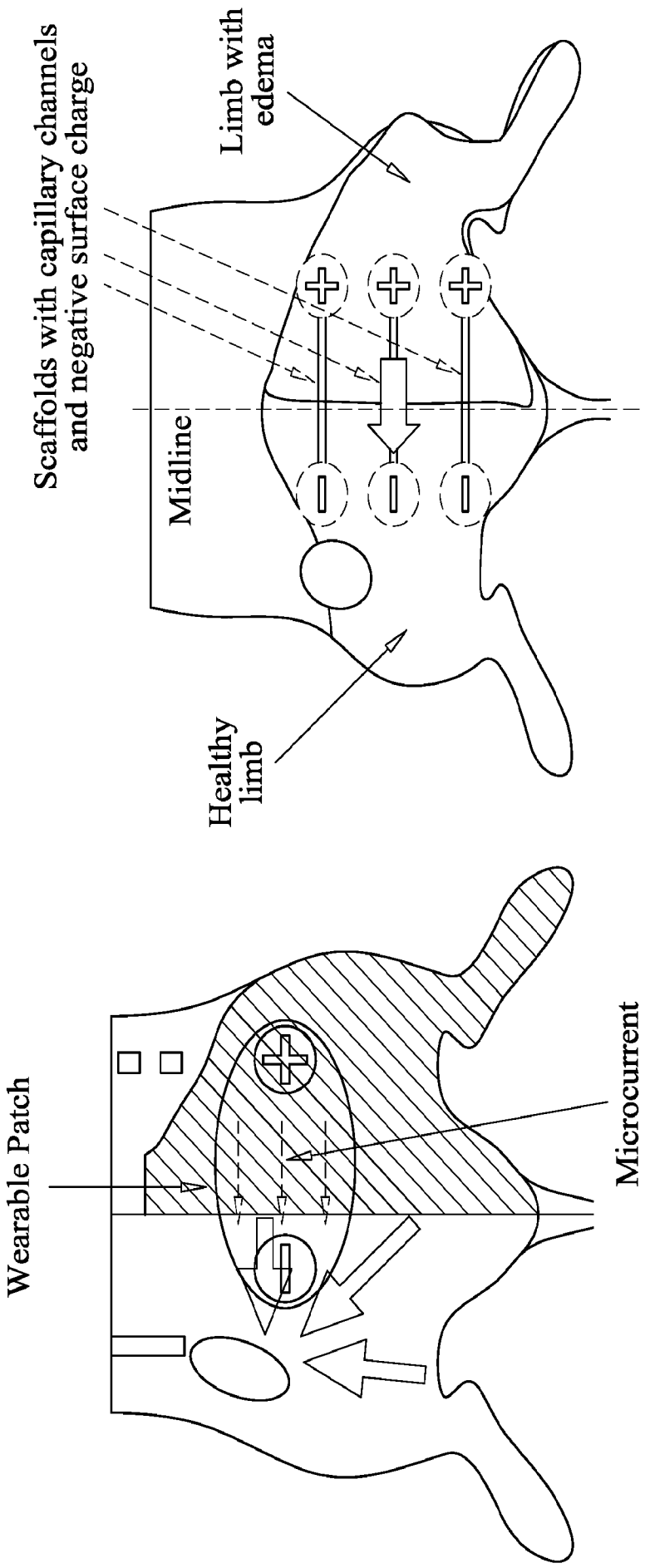

Scaffolds with capillary channels and negative surface charge
Limb with edema
Midline
Healthy limb
Wearable Patch
Microcurrent

FIG. 8

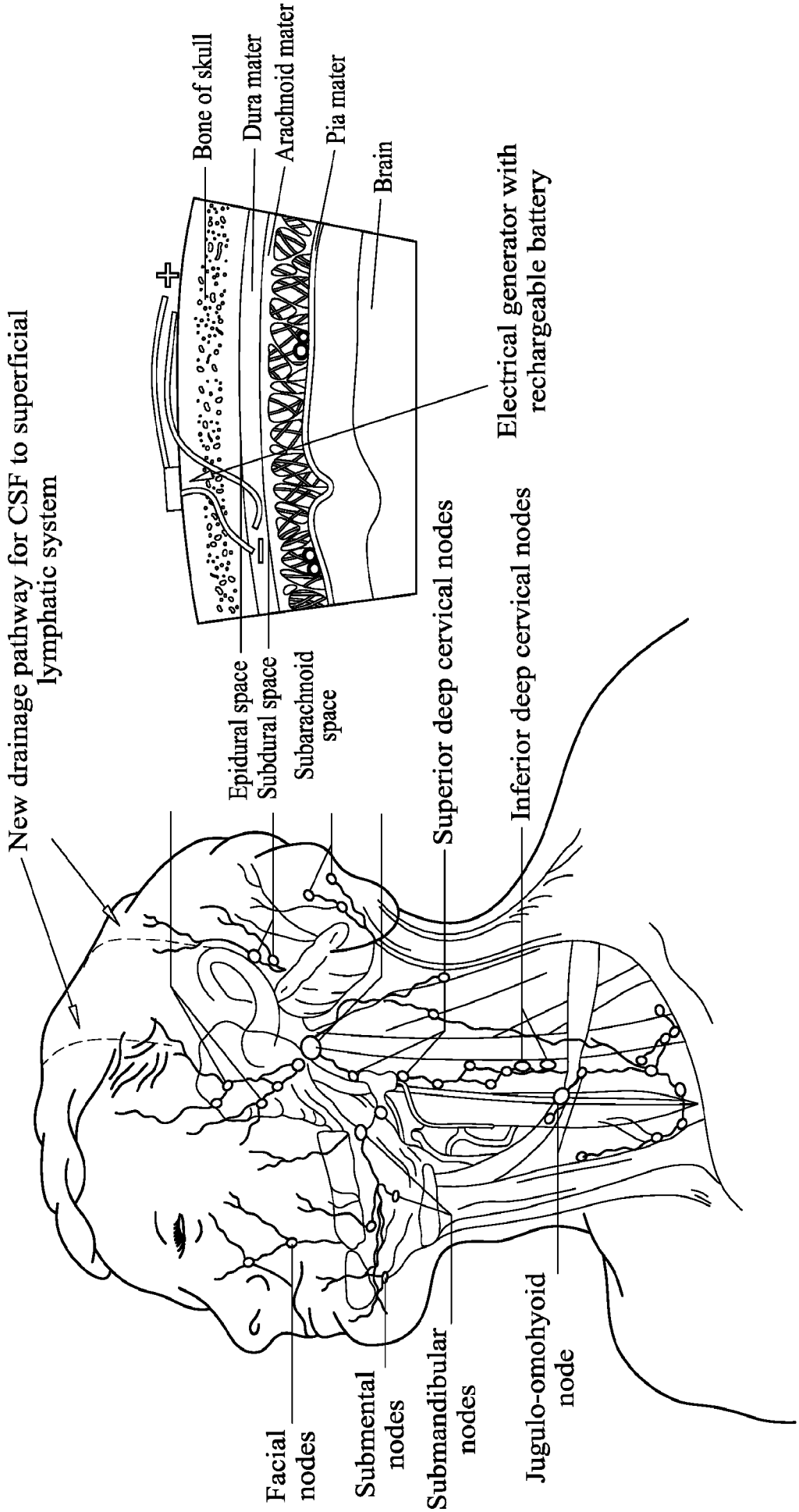

New drainage pathway for CSF to superficial lymphatic system
Bone of skull
Dura mater
Arachnoid mater
Pia mater
Brain
Electrical generator with rechargeable battery
Epidural space
Subdural space
Subarachnoid space
Superior deep cervical nodes
Inferior deep cervical nodes
Facial nodes
Submental nodes
Submandibular nodes
Jugulo-omohyoid node

FIG. 9

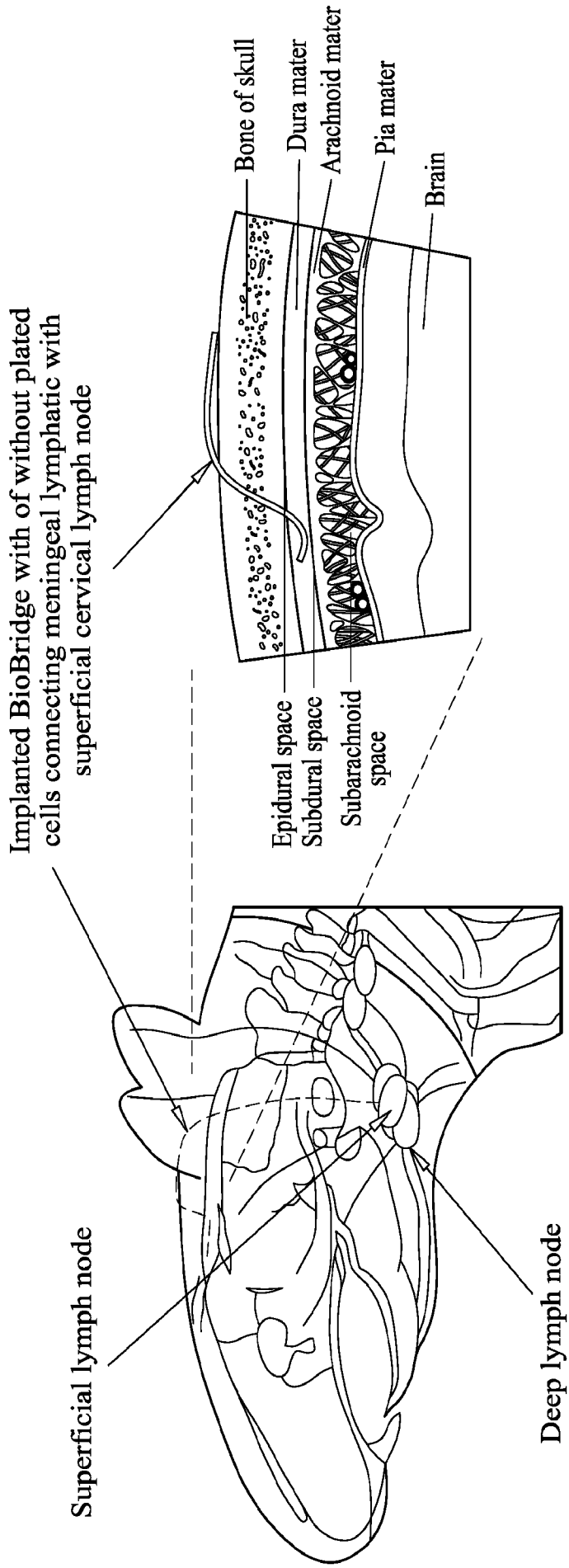

Implanted BioBridge with of without plated cells connecting meningeal lymphatic with superficial cervical lymph node
Bone of skull
Dura mater
Arachnoid mater
Pia mater
Brain
Epidural space
Subdural space
Subarachnoid space
Superficial lymph node
Deep lymph node

FIG. 10

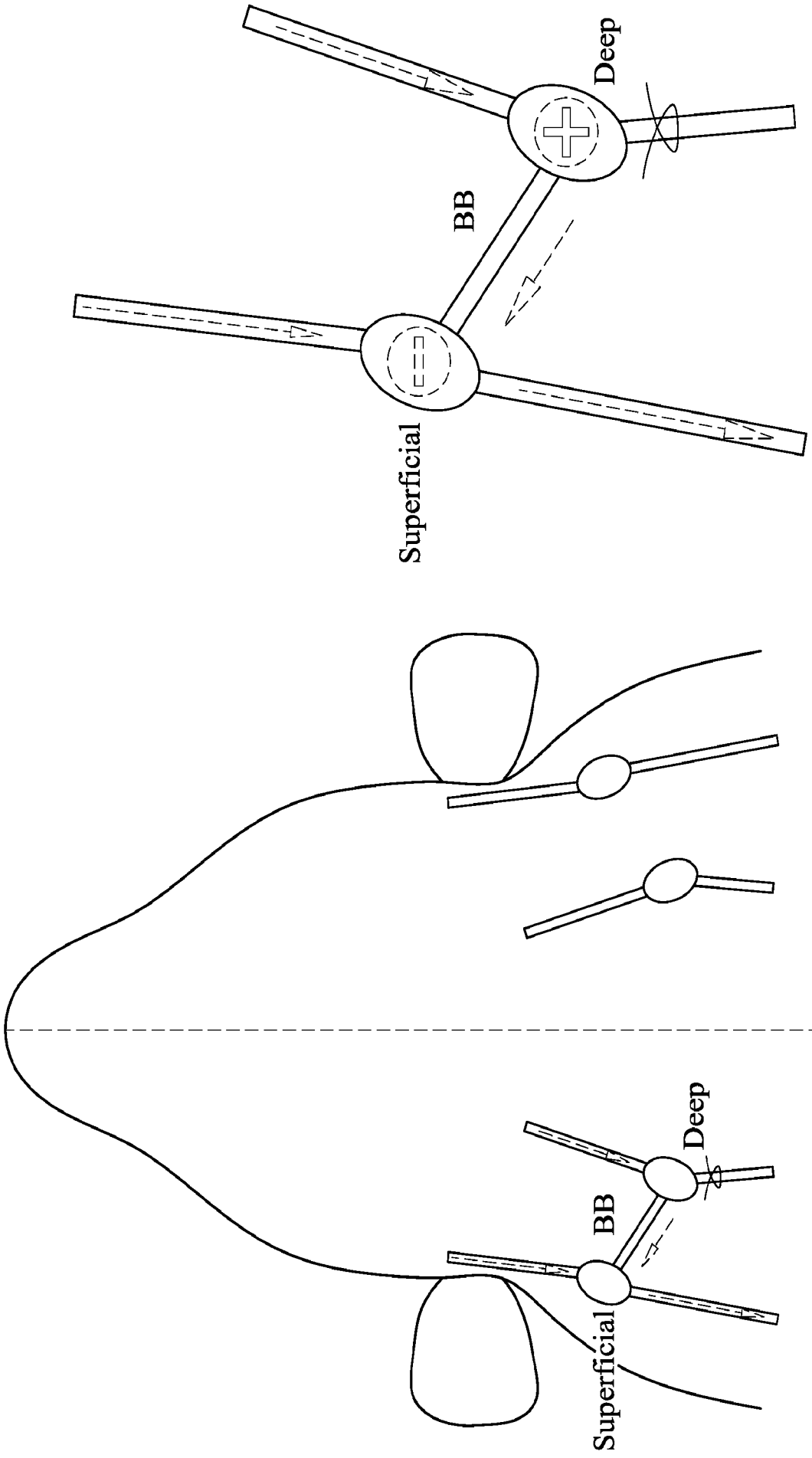


FIG. 11

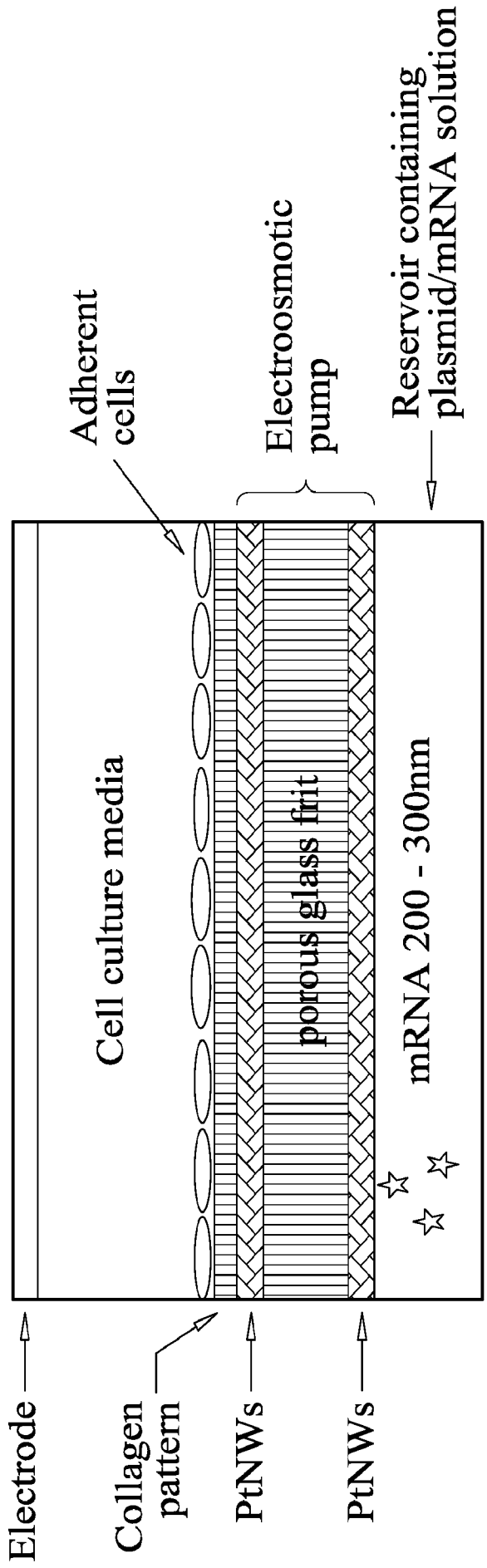

Adherent cells
Electroosmotic pump
Reservoir containing plasmid/mRNA solution
Cell culture media
porous glass frit
mRNA 200 - 300nm
Electrode
Collagen pattern
PtNWs
PtNWs

FIG. 12