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(54) **Title:** DISPOSABLE TUBING SET FOR USE WITH A CELL EXPANSION APPARATUS AND METHOD FOR STERILE SAMPLING

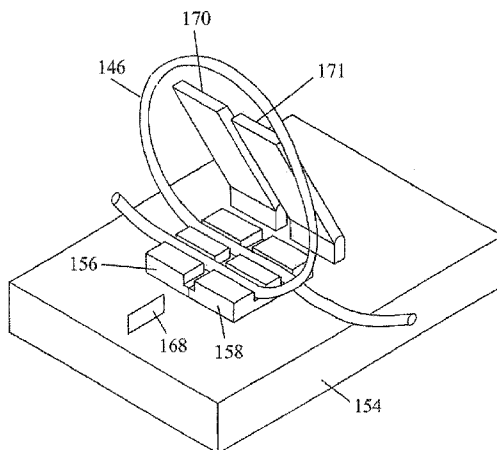


Figure 6

(57) **Abstract:** A disposable apparatus for cell expansion, having at least one bioreactor. The bioreactor has a cellular growth area and a supply area, the cellular growth area being separated from said supply area by a membrane. A fluid recirculation path in fluid communication with the cellular growth area allows for hermetically removing a sample containing cellular matter. This may comprise an elongated tube, or a plurality of parallel tube segments. The parallel tube segments have inflow ends and outflow ends, and the inflow ends are joined at a first common juncture and the outflow ends are joined at a second common juncture. The common junctures may comprise valves.

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DISPOSABLE TUBING SET FOR USE WITH A CELL EXPANSION APPARATUS AND METHOD FOR  
STERILE SAMPLING

The present invention is directed toward a disposable set adapted for use with a machine for cell expansion. The disposable set consists of at least a bioreactor or cell expansion module, an oxygenator and associated bags and tubing. A cassette to aid in organizing the tubes on the machine may also be included, as well as various drip chambers, sample ports and in line filters. The invention provides a method and apparatus for taking multiple sterile samples from a cell-containing part of the set. The apparatus may include a tube having multiple parallel tube segments, from which a selected segment can be removed without interrupting the flow of fluid within the disposable set.

#### BACKGROUND OF THE INVENTION

Stem cells can be expanded from a few donor cells in a cell expansion apparatus. The resulting multiplied cells can be used to repair or replace damaged or defective tissues. Stem cells have broad clinical applications for a wide range of diseases. Recent advances in the area of regenerative medicine have demonstrated that stem cells have unique properties such as high proliferation rates and self-renewal capacity, ability to maintain an unspecialized cellular state, and the ability to differentiate into specialized cells under particular conditions.

As an important component of regenerative medicine, bioreactor systems play an important role in providing optimized environments for cell expansion. The bioreactor provides efficient nutrient supply to the cells and removal of metabolites, as well as furnishing a physiochemical environment conducive to cell growth. In particular, foreign cells, such as air-borne pathogens, must be excluded from the cell-growth areas of the bioreactor. At the same time it is important to be able to obtain samples of the expanding stem cells to determine how much cellular growth has taken place. There remains a need for improved apparatus and methods for hermetically sampling expanding cellular material from cell-growth areas of a bioreactor, without environmental contamination.

#### SUMMARY OF THE INVENTION

The present invention comprises a disposable apparatus for cell expansion, having at least one bioreactor. The bioreactor has a cellular growth area and a supply area, the cellular growth area being separated from said supply area by a membrane. The membrane inhibits migration of cells from the cellular growth area to the supply area and permits migration of certain chemical compounds from the cellular growth area to the supply area and of certain other chemical compounds from the supply area to the cellular growth area. At least one oxygenator is in fluid communication with the supply area, and a plurality of bags is in fluid communication with the cellular growth area, the bags providing fluids to the cellular growth area. A fluid recirculation path is in fluid communication with the cellular growth area, the fluid recirculation path having means for hermetically removing a sample containing cellular matter.

The means for hermetically removing a sample may comprise an elongated tube, the length of the tube being long enough to permit at least one length containing a sample to be removed from the elongated tube. In another aspect of the invention, the means for hermetically removing a sample may comprise a plurality of parallel tube segments.

In yet another aspect, the parallel tube segments have inflow ends and outflow ends, and the inflow ends are joined at a first common juncture and the outflow ends are joined at a second common juncture. In yet another feature of the invention, the common junctures may comprise valves.

Another aspect of the invention comprises a method of expanding cellular matter, the method comprising providing at least one bioreactor, the bioreactor having a cellular growth area and a supply area, and the cellular growth area being separated from the supply area by a membrane, the membrane being adapted to inhibit migration of cells from said cellular growth area to said supply area and to permit migration of certain chemical compounds from said cellular growth area to said supply area and of certain other chemical compounds from said supply area to said cellular growth area. The method further comprises conducting a fluid containing cellular matter into the cellular growth area; providing oxygenated fluid to said supply area to maintain conditions conducive for cell growth in said cellular growth area; hermetically removing a sample containing cellular matter from a fluid recirculation path in fluid communication with said cellular growth area.

A further feature of the invention comprises providing an elongated tube, the length of the tube being long enough to permit at least one length containing the sample to be removed from the elongated tube; placing a loop of said elongated tube in a sealing device such that the tube forms an intersection with itself in said sealing device; severing the tube at said intersection to form two free ends of said tube and a looped tube segment having two ends; cauterizing the two ends of said tube segment; and sealing said two free ends of said tube together to re-connect said tube.

These and other features and advantages of the present invention will be apparent from following detailed description, taken with reference to the attached drawings and claims.

#### BRIEF DESCRIPTION OF THE DRAWINGS.

Figure 1 is a schematic description of a cell expansion apparatus.

Fig. 2 is a perspective view of a means for removing a cellular sample from a cell expansion side of a cell expansion apparatus.

Fig. 3 is a further perspective view of the means for removing a cellular sample, with a valve.

Fig. 4 Figure 4 is a further example of means for removing a fluid sample.

Fig. 5 is a perspective view of a coil of tubing.

Fig. 6 is a perspective view of a tubing sealer

Fig. 7 is a top view of a portion of the sealer of Fig. 6.

Fig. 8 is a further top view of the portion of the sealer of Fig. 7.

Fig. 9 is a further top view of the portion of the sealer of Figures 6 through 8.

#### DETAILED DESCRIPTION OF THE INVENTION

In the following description of the invention and in the accompanying drawings, like numerals refer to like parts.

### Cell expansion module

A cell expansion module **12**, or bioreactor, may be made of hollow fibers or flat sheet membranes enclosed in a housing. If hollow fibers are used, the fibers may be made of a biocompatible polymeric material such as Polyamix, which is a blend of polyamide, polyarylethersulfone and polyvinylpyrrolidone. Depending upon the type of cells to be expanded in the bioreactor, the fibers may or may not be treated with a substance to enhance cell growth and/or adherence to the membrane. The fibers may be held in place within the housing with polyethylene potting. The bioreactor housing has at least four openings into the interior of the housing. Two open into the intra-capillary or IC space, fluidly connecting to the interior of the hollow fibers, and two open into the extracapillary or EC space, fluidly connecting to the space surrounding the hollow fibers.

Cells may be grown in the IC space. The IC space with its minimum volume reduces the quantity of expensive media and expensive cytokines/growth factors required. The semi-permeable membrane allows transfer of metabolic components, waste and gases between the EC and IC compartments. The molecular transfer characteristics of the hollow fibers are chosen to minimize loss of expensive reagents from the IC side, while allowing metabolic waste products to diffuse through the membrane into the EC side to be removed. The EC space carries nutrients to the cells in the IC space, removes waste byproducts and maintains gas balance. The bioreactor may be attached to the rest of the disposable set with connectors made of polyurethane (Tygothane C-210-A).

### Oxygenator

The oxygenator **14** used may be any commercially available oxygenator. One alternative oxygenator that may be used is a hollow fiber Oxy-Cell Mate oxygenator having a fiber count of 1820, an internal fiber diameter of 280  $\mu\text{m}$ , an outer fiber diameter of 386  $\mu\text{m}$  and an intercapillary fluid volume of 16 mL. The hollow fibers of the oxygenator are enclosed in a housing having four port openings. Inlet **20** and outlet **46** ports are fluidly connected to the interior (intercapillary or IC space) of the hollow fibers. Another set of inlet

48 and outlet 50 ports are fluidly connected to the space surrounding the hollow fibers (extracapillary or EC space).

Through the IC inlet port 20 of the oxygenator, the EC inlet line 18 is connected to deliver either fresh media from the EC media bag 16 or recirculated EC media to the oxygenator 14. Connected to the IC outlet port 46, the EC line 18 delivers oxygenated EC media to the EC inlet port 42 on the bioreactor 12. Connected to the EC inlet port 48 is a line 52 to a source of gas 54 (gas line). The EC outlet port 50 is open to the atmosphere, with a 0.22  $\mu$  in-line filter 56 to prevent microbes from entering and contaminating the closed system.

#### EC media bag and EC media inlet line

An EC media bag 16, which contains the media, which will flow through the EC side of the bioreactor, may be connected via a portion of flexible tubing (the EC inlet line) 18 to the IC inlet port 20 of the oxygenator 14. The EC inlet line 18 brings fresh EC media to the oxygenator 14 to be oxygenated. The EC inlet line 18 may be made of polyvinyl chloride with fluorinated ethylene propylene (PVC/FEP (sold as Tygon SE-200)).

#### IC media bag and IC media inlet line

An IC media bag 22 that contains the media that will flow through the IC side of the bioreactor may be connected via a portion of flexible tubing (the IC inlet line) 24 to the IC inlet port 26 of the bioreactor 12. The IC inlet line 24 brings fresh IC media to the IC side of the bioreactor. The IC inlet line 24 may also be made of PVC/FEP.

#### Vent bag

A vent bag 28 may be connected to the disposable set via flexible tubing 27 to collect any air initially in the system, before the system is filled with media and cells.

#### Cell input bag

A cell input bag 30 contains the cells to be added to the bioreactor 12. The cell input bag 30 is connected to the IC inlet line 24, which delivers cells into the lumen of the hollow fibers via cell input line 29.

### Cell harvest bag

When the cells are ready to be harvested, they are flushed out of the IC outlet port **34** of bioreactor **12** through cell harvest line **31** and into a cell harvest bag **32**.

### IC Recirculation/reseeding tubing loop

The disposable tubing set also may include a length of tubing which acts as an IC circulation loop **36**. The IC media flows out of the bioreactor **12** from the IC outlet port **34** through tubing loop **36** and back into the bioreactor through the IC inlet port **26**. This loop **36** is used to recirculate the IC media through the hollow fibers. It may also be used to flush the cells out of the hollow fibers and reseed/redistribute them throughout the hollow fibers for further growth.

The IC recirculation loop **36** may contain a sample tube **38**, for example, an additional length of tubing. This additional tubing enables small pieces of the tubing to be sterilely removed from the disposable set and the media inside tested for markers of cellular metabolism such as pH, glucose, lactate, electrolytes, oxygen and carbon dioxide content. The sample tubing **38** may be made of Sanipure tubing (SEBS). The sample tube **38** may be solvent bonded into the IC loop **36** using cyclohexanone.

### EC recirculation loop

An EC recirculation loop **40** allows the media on the EC side of the bioreactor to be recirculated. The EC recirculation loop **40** allows EC media to flow out of the bioreactor from the EC outlet port **42** back into the bioreactor through the EC inlet port **44**. This loop may be used to recirculate the EC media that surrounds the hollow fibers.

### Waste bag

IC and EC media containing metabolic breakdown products from cell growth are removed from the system via tubing **58** into a waste bag **60**.

### Pump loops

As shown in FIG. 1, the tubing set may engage three or more pump loops that correspond to the location of peristaltic pumps on the cell expansion apparatus. In an embodiment, the tubing set may have five pump loops, corresponding to pumps **P1-P5** on the



apparatus. The pump loops may be made of polyurethane (PU (available as Tygothane C-210A)).

### Cassette

A cassette for organizing the tubing lines and which may also contain tubing loops for the peristaltic pumps may also be included as part of the disposable. Additional tubing lines (see **62**) can be added as needed to enable specific applications such as reseeded/redistributing cells in the bioreactor. In order to control the passage of fluid through the disposable **10**, manually operated clamps **64**, **66** may be provided. In addition, microprocessor-controlled pinch valves **68**, **70**, **72**, **74**, **76**, **80**, **82** may be coupled to selected tubes of the disposable. Microprocessor-controlled pinch valves are available on blood processing devices such as the Trima<sup>®</sup> apheresis machine, available commercially from the assignee of this invention. A Trima apheresis machine may be modified to accept the disposable **10** by removing a centrifuge ordinarily mounted within the Trima apheresis machine and placing the bioreactor and oxygenator within the machine as an incubator **81**. Temperature sensors **86**, **88**, **90** and pressure sensors **92**, **94**, and **96** can be connected to selected tubes of the disposable **10** and placed in electrical communication with a microprocessor (not shown). It is to be understood that pumps, temperature sensors, pressure sensors and pinch valves are preferably connected to the disposable set only temporarily by contact. Manual clamps, on the other hand, are usually mounted on their respective tubes and may be delivered with the disposable.

With the disposable apparatus **10** mounted in the incubator **81**, extracorporeal media is flowed throughout the apparatus **10**, including all connecting tubes, first and second drip chambers **98**, **100**, the oxygenator **14** and the bioreactor **12**. Pumps **P1**, **P2**, **P3** and **P4**, controlled by the incubator **18** may be selectively activated to force fluid into sections of the disposable apparatus to prime the apparatus. After priming, intercellular media and cells, for example mesenchymal stem cells may be added from bags **22**, **30** through the first drip chamber **98** and conducted into a cell expansion area of the bioreactor **14** and related tubing including recirculation path **36** and sample means **38**. The hermetically sealed condition of the apparatus **10** is maintained by providing a vent bag **28** coupled to the first drip chamber **98** to accommodate variations in flow from the EC media bag **16**, the IC media bag **22** and the cell input bag **30**. Driven by pump **P2**, extra corporeal fluid passes through the oxygenator **14** where the fluid is infused with gas into a supply area of the bioreactor **12**. The

supply area is separated from the cell expansion area by a membrane that allows oxygen and other desirable chemical components to pass into the cell expansion area and allows waste products of the cell expansion process to pass by osmosis out of the cell expansion area while preventing cellular matter from crossing the membrane. The status of the fluid flowing through the supply area of the bioreactor by temperature sensor **88** and pressure sensor **94** as well as temperature sensor **90**, which monitors the temperature of the fluid entering the oxygenator **14**. An appropriate gas, such as oxygen, or a gas mixture is conducted through the oxygenator **14** at a pressure monitored by sensor **96**. The gas is preferably medical grade and is also isolated from ambient air by 0.22 micron filters **56, 57**. The characteristics of the extracorporeal fluid can also be checked by withdrawing fluid samples through sample ports **S1** and **S2** on the inflow and outflow lines of the bioreactor. The sample ports have internal filters that allow fluid to be extracted by cellular sized particles from passing into or out of the apparatus **10**.

The pumps are preferably peristaltic pumps. In addition to the manual clamps and automatically controlled valves, the pumps also act as valves, preventing flow of fluid past the pump when the pump is not actively driven. Therefore, when pump **P1** is not in operation and valves **76, 78** are closed, a recirculation loop is formed through the bioreactor **12** and pump **P4**. Conditions in this recirculation loop, where cells are growing, are monitored with temperature sensor **86** and pressure sensor **92** and by taking fluid samples through a sample port **S3**. The fluid extracted through the sample port **S3**, as explained above, does not contain cells or particles of cellular size. It is important to be able to monitor the progress of cellular growth over time without compromising the hermetically sealed conditions of the apparatus **10**. Once the desired cell concentrations have been obtained, the contents of the bioreactor **12** can be harvested into the cell harvest bag **32**.

The sample tube **38** allows discrete samples of cell-containing fluid to be removed from the cell expansion area from time to time. The samples may then be tested to determine the state of cell growth in the cell expansion area. One embodiment of a sample tube **38** is illustrated in greater detail in Fig. 2. The sample tube **38** comprises two or more branches **110, 112, 114**. One or more of the branches may be provided with a releasable clamp **116** for temporarily stopping fluid flow through the selected branch. Alternatively, other closure means, such as a hemostat, could be used. Preferably, flow is directed through a selected branch **114** by stopping the flow through other branches. When a stable flow has been

established such that the contents of the selected branch reasonably represent the general contents of fluid in the cell expansion area, at least one other branch may be opened and the selected branch closed. This maintains flow through the tubing. The selected branch **114** can then be removed by application of an RF sealer (not shown) at opposite ends **118, 120** of the branch. The resulting tube segment contains a fluid sample, preferably about 1 mL in volume. Both the tube segment and the remaining portions of the apparatus **10** remain hermetically sealed.

It is not necessary to remove a complete branch to obtain a sample. The branches may be made long enough such that multiple samples can be taken. In a preferred embodiment comprising two branches, a sample may be taken from a first branch that is closed by a clamp or hemostat, while fluid continues to flow through a second branch. The free ends of the first branch are re-connected, as further described below. When a second sample is to be taken, the clamp or hemostat could be placed on the second branch, the sample could be removed, and the free ends of the second branch could be re-connected, in the same manner as the first branch. Additional samples could then be taken, alternating between the first and second branches. This maintains a similar length for both branches. Moreover, since fluid flow in both branches is restored between samples, there is little likelihood of a stagnant area forming in the flow path.

In an alternative embodiment shown in Fig. 3, a valve **122** may be substituted for the clamp **116**.

The branches **110, 112, 114** may join at common junctions **124, 126**, as shown in Fig. 2, or may be spaced serially around a central tube **128**, as shown in Fig. 4. A first branch **130** may exit the central tube **128** at a first outlet **132** and return to the central tube at a first inlet **134**. A second branch **136** may exit the central tube at a second outlet **138**, spaced linearly downstream from the first outlet **132** and radially displaced around the tube from the first outlet. The second branch **136** may return to the central tube at a second inlet **140**, likewise downstream and radially displaced from the first inlet **134**. This pattern may be replicated for a third branch **142**, a fourth branch **144**, and so on for as many branches as desired. A branch may be removed for a sample by cauterizing the branch near its outlet and inlet, as explained above.

A further embodiment, illustrated in Figures 5 through 9, comprises a method for removing a tube segment containing a cellular sample from an elongated tube. As shown in Fig. 5, the sample tube 38 may be elongated substantially more than necessary to connect apparatus in the disposable set 10. The additional length of the tube may be stored in a plurality of loops 146, 148, 150, 152. When a sample containing cellular material is needed, a loop 146 is placed in a tubing welder 154, such as tubing welders available from Terumo Medical Corporation, Somerset, New Jersey. The welder 154 may have slidable tube supports 156, 158, which have parallel slots for receiving tubes. Initially, slots 160 and 162 in a first tube support 156 are aligned with slots 164 and 166 in second tube support 158. Latches 170, 171 are closed over the respective tube supports 156, 158, holding the tube and its loop 146 in place. The latches 170, 171 are not shown in Figures 7, 8 and 9, to more clearly show the position of the tube. A disposable copper welding wafer is inserted into a gap 172 between the tube supports 156, 158 from a magazine (not shown) in the tubing welder 154. The wafer is electrically heated to cut, cauterize and seal the ends of the tube. With the heated wafer dividing the tube, the loop 146 containing the desired sample can be removed from the welder. The supports 156, 158 are then offset until a second slot 162 of the first support 156 aligns with a first slot of the second support 158, whereby cut ends 174, 176 of the tube are adjacent each other. The wafer 168 can then be removed and heated ends of the tube melt together. Fluid can then resume flow in the tube. Additional samples may be taken from time to time as long as there is sufficient length of tube to form the required loop.

The described apparatus and method can be used to collect a fluid sample containing cellular matter from a cellular expansion system. When sufficient cell replication has taken place, as determined by analysis of the sample, the contents of the bioreactor can be harvested into the cell harvest bag 32. The expanded cellular material would then be available for therapeutic and other purposes.

The foregoing description of the present invention has been presented for purposes of illustration and description. Furthermore, the description is not intended to limit the invention to the form disclosed herein. Consequently, variations and modifications commensurate with the above teachings, and skill and knowledge of the relevant art, are within the scope of the present invention. The embodiments described hereinabove are further intended to explain best modes known of practicing the invention and to enable others skilled in the art to utilize the invention in such, or other embodiments and with various

modifications required by the particular application(s) or use(s) of the present invention. It is intended that the appended claims be construed to include alternative embodiments to the extent permitted by the prior art.

## CLAIMS

I claim

1. A disposable apparatus for cell expansion, said apparatus comprising  
at least one bioreactor, said bioreactor having a cellular growth area and a supply area, said cellular growth area being separated from said supply area by a membrane, said membrane being adapted to inhibit migration of cells from said cellular growth area to said supply area and to permit migration of certain chemical compounds from said cellular growth area to said supply area and of certain other chemical compounds from said supply area to said cellular growth area;  
at least one oxygenator in fluid communication with said supply area;  
a plurality of bags in fluid communication with said cellular growth area, said bags being adapted to provide fluids to said cellular growth area;  
a fluid recirculation path in fluid communication with said cellular growth area, said fluid recirculation path having means for hermetically removing a sample containing cellular matter.
2. The disposable apparatus of claim 1 wherein said means for hermetically removing a sample comprise an elongated tube, the length of said tube being long enough to permit at least one length containing said sample to be removed from said elongated tube.
3. The disposable apparatus of claim 1 wherein said means for hermetically removing a sample comprise a plurality of parallel tube segments.
4. The disposable apparatus of claim 3 wherein said parallel tube segments having inflow ends and outflow ends, and said inflow ends are joined at a first common juncture and said outflow ends are joined at a second common juncture.
5. The disposable apparatus of claim 4 wherein said common junctures comprise valves.
6. The disposable apparatus of claim 1 further comprising at least one sample port, said sample port being adapted to allow sampling of non-cellular matter from said apparatus.
7. A method of expanding cellular matter, said method comprising

providing at least one bioreactor, said bioreactor having a cellular growth area and a supply area, said cellular growth area being separated from said supply area by a membrane, said membrane being adapted to inhibit migration of cells from said cellular growth area to said supply area and to permit migration of certain chemical compounds from said cellular growth area to said supply area and of certain other chemical compounds from said supply area to said cellular growth area;

conducting a fluid containing cellular matter into said cellular growth area;

providing oxygenated fluid to said supply area to maintain conditions conducive for cell growth in said cellular growth area;

hermetically removing a sample containing cellular matter from a fluid recirculation path in fluid communication with said cellular growth area.

8. The method of claim 7 further comprising providing an elongated tube, the length of said tube being long enough to permit at least one length containing said sample to be removed from said elongated tube;

placing a loop of said elongated tube in a sealing device such that said tube forms an intersection with itself in said sealing device;

severing said tube at said intersection to form two free ends of said tube and a looped tube segment having two ends;

cauterizing the two ends of said tube segment; and

sealing said two free ends of said tube together to re-connect said tube.

9. The method of claim 7 further comprising

providing a plurality of parallel tube segments;

flowing fluid containing cellular matter through at least a first segment;

interrupting flow through said first segment while simultaneously flowing said fluid through a second segment; and

hermetically removing said first segment.

10. The method of claim 9 wherein said parallel tube segments having inflow ends and outflow ends, and said inflow ends are joined at a first common juncture and said outflow ends are joined at a second common juncture.

11. The method of claim 10 wherein said common junctures comprise valves.

12. The method of claim 7 further comprising sampling non-cellular matter from said apparatus at at least one sample port, said sample port being adapted to allow only non-cellular matter to be sampled.
13. A cellular expansion system comprising  
a disposable apparatus comprising  
at least one bioreactor, said bioreactor having a cellular growth area and a supply area, said cellular growth area being separated from said supply area by a membrane, said membrane being adapted to inhibit migration of cells from said cellular growth area to said supply area and to permit migration of certain chemical compounds from said cellular growth area to said supply area and of certain other chemical compounds from said supply area to said cellular growth area;  
at least one oxygenator in fluid communication with said supply area;  
a plurality of bags in fluid communication with said cellular growth area, said bags being adapted to provide fluids to said cellular growth area;  
a fluid recirculation path in fluid communication with said cellular growth area, said fluid recirculation path having means for hermetically removing a sample containing cellular matter; and  
an incubator for receiving said disposable apparatus said incubator having means for controlling flow of fluids within said bioreactor.
14. The cellular expansion system of claim 13 wherein said means for hermetically removing a sample comprise an elongated tube, the length of said tube being long enough to permit at least one length containing said sample to be removed from said elongated tube.
15. The cellular expansion system of claim 13 wherein said means for hermetically removing a sample comprise a plurality of parallel tube segments.
16. The cellular expansion system of claim 15 wherein said parallel tube segments having inflow ends and outflow ends, and said inflow ends are joined at a first common juncture and said outflow ends are joined at a second common juncture.



17. The cellular expansion system of claim 16 wherein said common junctures comprise valves.
  
18. The cellular expansion system of claim 13 further comprising at least one sample port, said sample port being adapted to allow sampling of non-cellular matter from said apparatus.



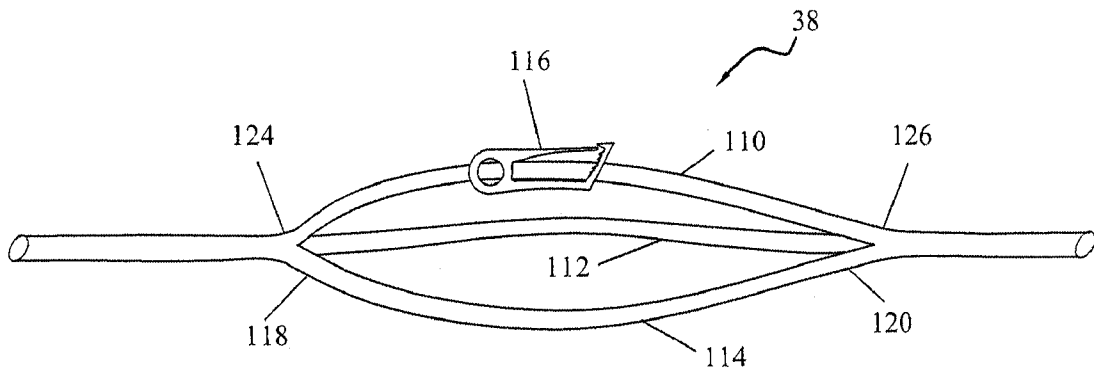


Figure 2

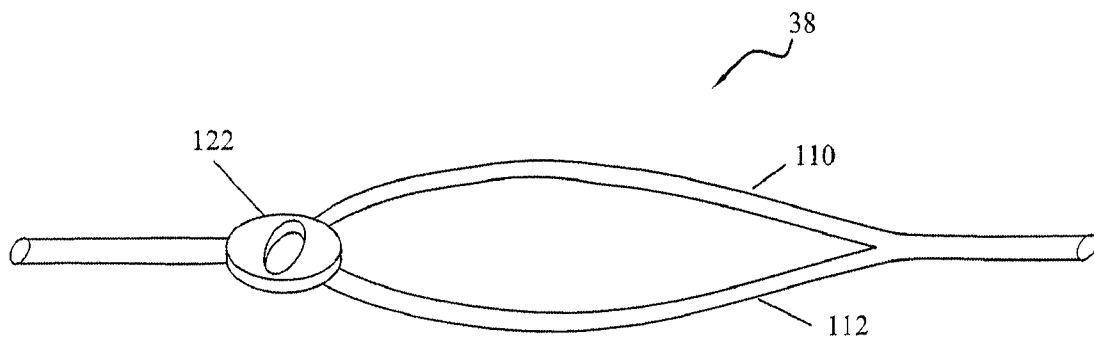


Figure 3

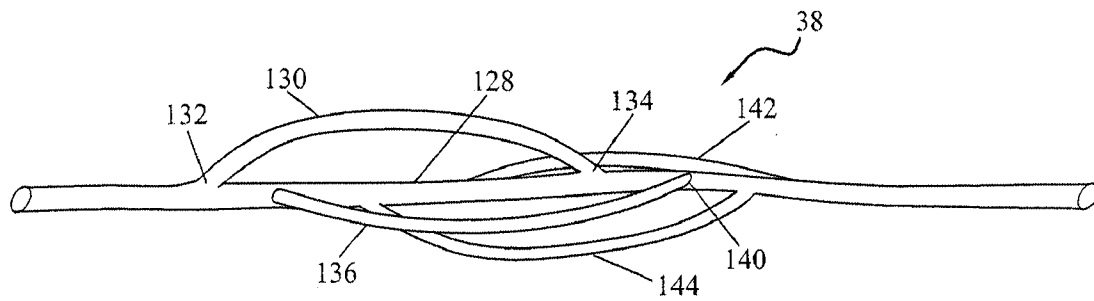


Figure 4

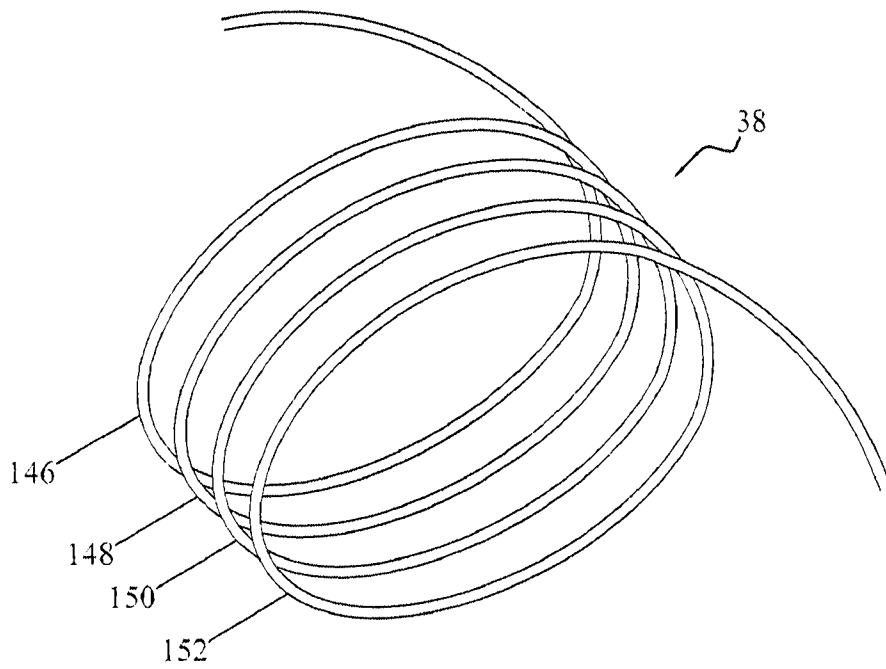


Figure 5

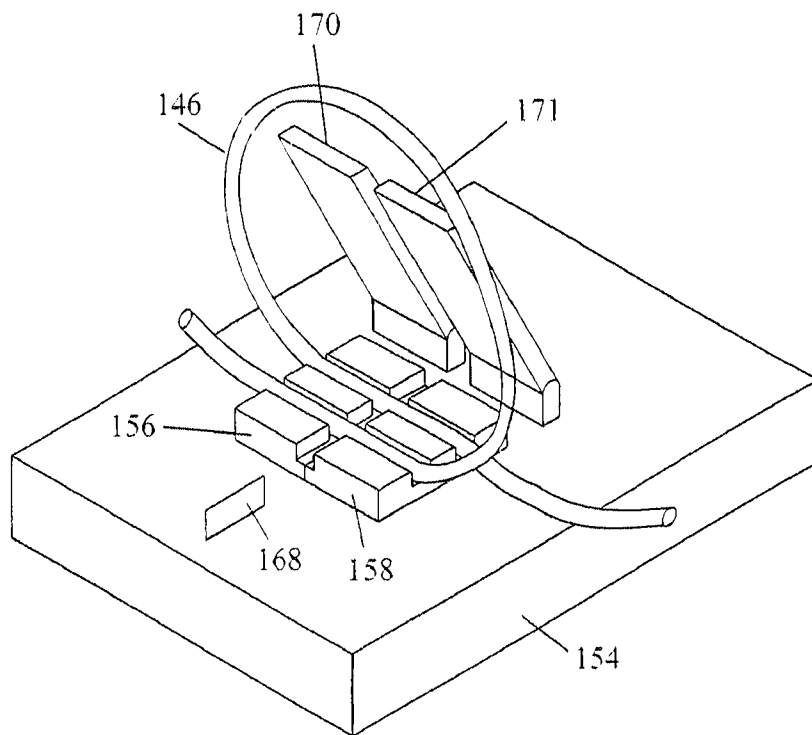


Figure 6

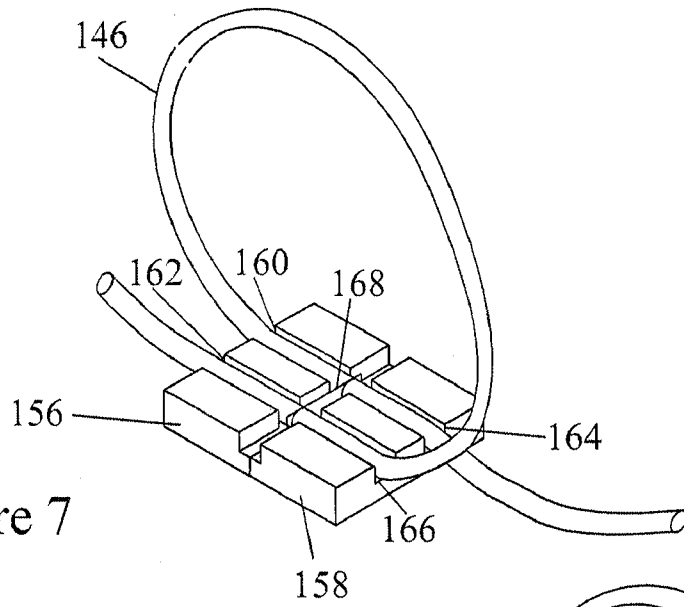


Figure 7

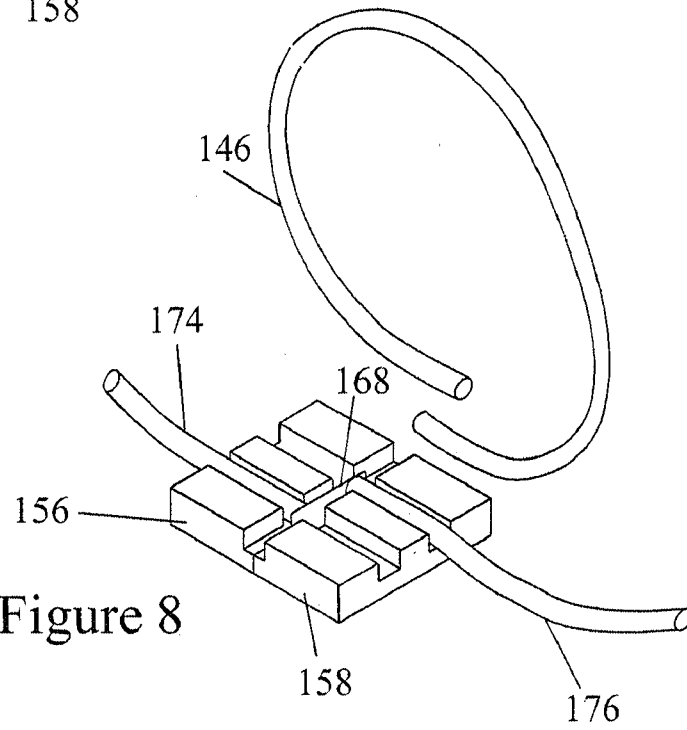


Figure 8

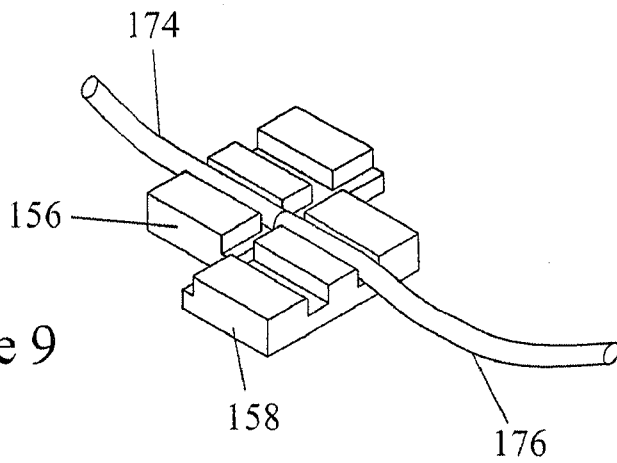


Figure 9

# INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2008/052185

**A. CLASSIFICATION OF SUBJECT MATTER**  
INV. C12M1/26

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

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
C12M

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)  
EPO-Internal

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/28996 A (CANNON THOMAS F [US]; COHN LAURA K [US]; QUINN PETER D [US]) 11 April 2002 (2002-04-11) paragraph [0013] - paragraph [0057]; figure 7	1
X	WO 2006/026835 A (UNISEARCH LTD [AU]; GAMBRO LUNDIA AB [SE]; NORDON ROBERT [AU]; DORAN M) 16 March 2006 (2006-03-16) page 6, line 8 - line 27; figure 2	1
A	US 2002/146816 A1 (VELLINGER JOHN C [US] ET AL) 10 October 2002 (2002-10-10) paragraph [0056] - paragraph [0057]	1
A	WO 03/092573 A (GAMBRO INC [US]) 13 November 2003 (2003-11-13) page 10, line 24 - page 15, line 5	1

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

\* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
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- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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- \* & \* document member of the same patent family

Date of the actual completion of the international search  <b>25 June 2008</b>	Date of mailing of the international search report  <b>03/07/2008</b>
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer  <b>Clement, Jean-Paul</b>
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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No PCT/US2008/052185
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Patent document cited in search report	Publication date	Publication date	Patent family member(s)	Publication date
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