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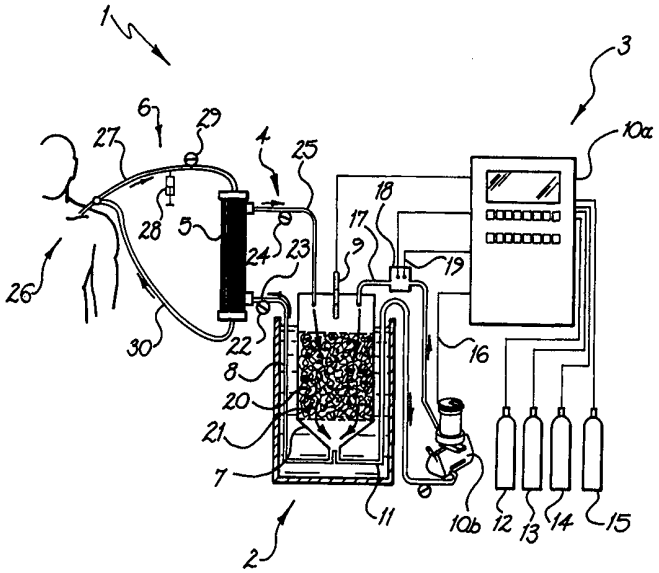
(54) Title: A BIODIALYSIS SYSTEM FOR LIVER SUPPORT



(57) Abstract

This invention concerns a liver support system. In particular, it concerns a bioartificial liver support system which operates by liver biodialysis, or blood filtrate or plasma biomodulation. This involves a bioreactor in which hepatocytes are maintained in culture. An exchange barrier having two sides. A first circuit which is arranged to carry fluid from the bioreactor to a first side of the exchange barrier and back. And a second circuit which is arranged to carry blood from a patient to the second side of the exchange barrier and back.

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A BIODIALYSIS SYSTEM FOR LIVER SUPPORT

Technical Field

This invention concerns a liver support system. In particular, it concerns a bioartificial liver support system which operates by liver biodialysis, or blood filtrate or plasma biomodulation.

Background Art

During the last ten years a number of bioartificial liver support systems have been developed to support patients with liver failure. These systems have living hepatocytes in contact with semi-permeable membranes, usually in the form of hollow fibres or flat plates. The patient's blood, plasma or serum passes or is pumped to place it in contact with the other side of the membrane. The pore size of the membrane determines the transport of molecules between the patient's blood and the hepatocytes. Toxic molecules accumulating in the blood of patients with liver failure, pass across the membrane to be metabolised by the hepatocytes, so detoxifying the patient's blood. Hepatocyte-synthetised products will pass in the opposite direction across the membrane to the patient's blood stream.

Such bioartificial liver support systems have a number of significant disadvantages. The hepatocytes attached to the outside of the semi-permeable membrane are in inferior culture conditions and are limited in number. Their presence inhibits the free transfer of molecules across the membrane. As well, close contact between the patient's blood, plasma or serum, and the hepatocytes facilitates allo- or xeno-reactions which adversely affect the hepatocytes. The effect of both the poor culture conditions and the immune reactions is to cause a progressive decline in the detoxifying and synthetic cell functions, resulting in diminishing performance. There is also a steadily increasing rate of death of hepatocytes which results in release of cell breakdown products and debris which can have access back across the membrane to the patient's blood stream.

If the pore size of a semi-permeable membrane is sufficiently large to allow passage from the blood of important large-molecule toxic metabolites, it will also be sufficiently large to allow passage back into the patient's blood stream of toxic metabolites, infective agents including feared viruses and cells or cell debris. These effects add danger to the treatment. As a result

treatment is often limited to 6-8 hour intermittent periods each day or second day, which are inadequate. Fresh hepatocytes must be provided for repeat treatments and the logistics of providing this are severe.

On the other hand, if the pore size is sufficiently small to prevent return of noxious agents to the patient's blood, then large-molecule toxic metabolites resulting from liver failure will not pass across the membrane from the blood for hepatocyte metabolism, making treatment less effective.

Finally, if intrafibre clotting occurs, then the entire cartridge with its contained hepatocytes must be discarded.

Statement of the Invention

The invention, as currently envisaged, is an artificial liver support system, including:

A bioreactor in which hepatocytes are maintained in culture. An exchange barrier having two sides. A first circuit which is arranged to carry fluid from the bioreactor to a first side of the exchange barrier and back. And a second circuit which is arranged to carry blood from a patient to the second side of the exchange barrier and back.

Such a system separates the patient's blood stream from the hepatocytes, which diminishes the opportunity for allo- or xeno-reactions and increases the safety of the system.

The bioreactor may have an associated computerised control system. The bioreactor may also include a containment vessel maintained at constant temperature in a water bath or otherwise. A temperature probe may report the temperature of the containment vessel to the computer system to allow feedback control of the temperature.

A gas exchanger may receive fluid from the bioreactor, and inject oxygen, carbon dioxide, nitrogen and air in doses measured by the computer system. A dissolved oxygen probe may provide a measure of dissolved oxygen to the computer system to allow feedback control of the gases.

A pH probe may provide a measure of pH to the computer system to allow feedback control of pH by adjustment of carbon dioxide flow.

In this way disorders of the patient's pH and blood gas concentrations, which are common in fulminant hepatic failure, may also be influenced by manipulation of the system.

Within the bioreactor vessel, primary animal or human hepatocytes or animal or human hepatocyte-derived cell lines may be attached to a polyester or other suitable matrix and bathed in fluid which could be plasma, serum, blood filtrate or other culture medium.

Ports may be provided for connection to the first circuit , and for monitoring, sampling, variation and removal of the contents of the bioreactor.

The bioreactor may culture the hepatocytes in large and sometimes life sustaining numbers in culture conditions which permit cell survival and function for an interval which may be several hours to several days or weeks. Enhanced viability and function of the hepatocytes provide improved detoxification of the patient's blood, plasma or serum and improved synthesis of needed substances. Furthermore, since the cells remain in good condition, there is greatly reduced cell death and disintegration, with resulting diminished release of dangerous products. Dead hepatocytes, their breakdown products and cell debris are able to settle to the bottom of the bioreactor from where they may be easily cleared.

The continued viability and function of the cells allow prolonged use of the equipment in patient treatment up to and including continuous treatment for hours, days or weeks without replacement of the hepatocytes. The overall effect is to improve the logistics and efficacy of treatment.

Fluid from the bioreactor may be pumped through the first circuit to circulate in a reverse direction through the extra-fibre compartment of a dialysis cartridge, and is then returned to the bioreactor. Blood may pass or be pumped through the second circuit from the patient in the forward direction through the hollow fibres of the dialysis cartridge, and is then returned to the patient.

For increased safety and to achieve enhanced metabolism of toxic molecules, a subsidiary circuit may be incorporated into the system. Detoxified filtrate from the bioreactor may be directed through a second dialysis cartridge, and filtrate from the second cartridge may then pass on to the first cartridge or be returned to the patient.

The use of subsidiary circuits permits viruses and other infective agents to be continuously cleared from the patient's circulation. Also, infective agents from the bioreactor may be prevented from accessing the patient's circulation.

The semi-permeable membrane pore sizes of the second cartridge may be smaller than those of the first cartridge. The smaller pores may prevent access of large molecule toxic or infective agents to the patient, and allow enhanced metabolism of the toxic molecules from the patient's blood because of recirculation through the bioreactor. The larger pore sizes of the first cartridge may allow passage of large molecule toxic products from the patient's blood.

Plasma proteins and coagulation factors may be administered separately by intravenous infusion.

A third dialysis cartridge may be added to receive the modulated filtrate emerging from the second cartridge and filter it again before passing it to the first cartridge.

In an alternative, blood from the patient may circulate through a dialysis cartridge or an apherisis system. Blood filtrate may be pumped from the dialysis cartridge, or apherisis system, to the bioreactor. Detoxified fluid containing hepatocyte-synthesised molecules may be returned directly to the patient from the bioreactor after traversing an in-line millipore bacterial filter.

Such a system may also be enhanced by returning the detoxified filtrate from the bioreactor through a subsidiary dialysis cartridge.

A charcoal filter may be included on the outflow line from the dialysis cartridge or apherisis system to the bioreactor.

The equipment can be used in much the same way as that for artificial kidney treatment for patients with renal failure, or that for patients requiring plasmapheresis, and has the same alarms and protective devices. This greatly facilitates usage as medical and paramedical personnel are fully familiar with artificial kidney and plasmapheresis treatments.

Anticoagulation may be no more than is required for haemodialysis or plasmapheresis and in many patients may not be necessary. In the event of clotting, the cartridge or the disposable items of the apherisis system can be replaced without interference with the hepatocytes. Haemodialysis can be incorporated into the system for patients with concurrent renal failure, a frequent complication of fulminant hepatic failure.

In another aspect, as currently envisaged, the invention is a method of processing blood, including the steps of:

Maintaining hepatocytes in culture in a bioreactor;

Carrying fluid from the bioreactor to the first side of an exchange barrier having two sides, and back to the bioreactor;

Carrying blood from a patient to the second side of the exchange barrier and back to the patient;

Transporting the constituents of the patient's blood which have increased concentration, when compared to the levels in the fluid circulated through the bioreactor, and which include fulminant hepatic failure toxic metabolites, from the patient's blood through the exchange barrier; and

Metabolising the toxic fulminant hepatic failure metabolites in the bioreactor.

Transporting hepatocyte-synthesised substances from the bioreactor fluid to the patient.

Brief Description of the Drawings

Several examples of the invention will now be described with reference to the accompanying drawings, in which:

Figure 1 is a schematic diagram of a liver biodialysis system embodying the present invention;

Figure 2 is a schematic diagram of an enhanced version of the liver biodialysis system of Figure 1;

Figure 3 is a schematic diagram of a further enhanced version of the liver biodialysis system of Figures 1 and 2;

Figure 4 is a schematic diagram of a blood filtrate or plasma biomodulation system embodying the present invention;

Figure 5 is a schematic diagram of an alternative blood filtrate or plasma biomodulation system embodying the present invention; and

Figure 6 is a schematic diagram of an enhanced version of the blood filtrate or plasma biomodulation system of Figure 4.

The same reference numerals have been used throughout the drawings to refer to corresponding elements.

Best Modes for Carrying Out the Invention

Liver biodialysis

Referring first to Figure 1, liver support system 1 includes a bioreactor 2 having a computerised control system indicated generally at 3.

Fluid from the bioreactor 2 is pumped through a circuit indicated generally at 4 to circulate in a reverse direction through the extra-fibre compartment of a dialysis cartridge 5. A second circuit indicated generally at 6 passes or pumps blood from the patient through the hollow fibres of the dialysis cartridge 5.

The bioreactor includes a containment vessel 7 maintained at constant temperature in a water bath 8. A temperature probe 9 reports temperature to a computer system 10a to allow feedback control of the temperature of the water bath.

A gas exchanger 10b receives fluid from the bioreactor 2 via line 11, and injects oxygen, carbon dioxide, nitrogen and air from bottles 12, 13, 14 and 15 respectively, via line 16, in doses measured by computer system 10a and 10b. Fluid from the gas exchanger 10b is returned to the top of the bioreactor by line 17. A dissolved oxygen probe 18 provides a measure of dissolved oxygen to the computer system 10a, and a pH probe 19 provides a measure of pH to the computer system 10a to allow feedback control of these variables.

Within the bioreactor vessel 7, primary human or animal hepatocytes or animal hepatocyte-derived cell lines are attached to polyester discs or other suitable matrix and bathed in appropriate fluid.

Ports are provided for connection to circulation systems, and for monitoring, sampling, variation and removal of the contents of the bioreactor 2.

In use, fluid is pumped by pump 22 from the bioreactor via line 23 to the dialysis cartridge 5. Line 23 may incorporate a blood transfusion filter. The fluid flows through the extra-fibre compartments of the cartridge, and returns from the cartridge to the bioreactor via line 25, helped, if needed, by pump 24.

At the same time blood from the patient 26 is drawn along line 27 and, if required, mixed with anti-coagulant from pump 28, before passing, or being pumped by pump 29 into the dialysis cartridge 5. The patient's blood circulates through the hollow fibres of the dialysis cartridge, dialysing across a semi-permeable membrane against the fluid from the bioreactor which is circulating in the opposite direction. Blood is then returned to the patient along line 30. The directions of the circulations from the patient and from

the bioreactor through the dialysis cartridge may be reversed without consequence to the objectives.

The constituents of the patient's blood which have increased concentration, when compared to the levels in the fluid circulated through the bioreactor, and which include fulminant hepatic failure toxic metabolites, pass from the patient's blood through the pores of the hollow fibres into the extra-fibre fluid and are pumped back to the bioreactor. In the bioreactor, hepatocytes metabolise the toxic fulminant hepatic failure metabolites and the detoxified fluid returns to the extra-fibre compartments of the dialysis cartridge for further exposure across the semi-permeable membrane to the patient's blood.

The hepatocytes in the bioreactor, as well as detoxifying, also synthesise molecules such as proteins, enzymes, carrier molecules and coagulation factors. As a result these molecules are at increased concentration in the circulating bioreactor fluid, and therefore pass across the semi-permeable membrane in the cartridge into the patient's blood.

For increased safety and to achieve enhanced metabolism of toxic molecules, a subsidiary circuit 31 can be incorporated into the liver biodialysis system as shown in Figure 2. By occluding tap 32 and releasing tap 33, detoxified fluid from the bioreactor 2 is directed through the hollow fibres of dialysis cartridge 34 and recirculates to the bioreactor via line 35. Filtrate from the extra-fibre compartment of cartridge 34 passes to the extra-fibre compartment of dialysis cartridge 5 along line 36 where it dialyses against the patient's blood before returning to the bioreactor along line 25.

If the semi-permeable membrane pore sizes of cartridge 34 are small, the subsidiary circuit 31 acts as a safety device preventing access of large molecule toxic or infective agents to the patient from the bioreactor, or such as might occur in the event of rupture of fibres of cartridge 5. It also allows enhanced metabolism of the toxic molecules from the patient's blood because of recirculation through the bioreactor.

If cartridge 34 has a pore size less than that of cartridge 5, selective removal of molecules from the patient's blood occurs with trapping in the bioreactor subsidiary circuit 31. Thus if the dialysis cartridge 5 has large pore sizes which allow passage of large molecules, and dialysis cartridge 34 semi-permeable membrane has small pore sizes which prevent the passage of large-molecules, large-molecule toxic products and infective agents with

sizes greater then the semi-permeable membrane pore sizes of cartridge 34 are continuously removed from the patient's plasma and returned to the bioreactor. Together with cells, cell debris and infective agents from the bioreactor the noxious agents are trapped in the subsidiary circuit and prevented from passing to the patient. Again, the detoxification of the blood is greatly enhanced because of recirculation through the bioreactor.

In such a system some large-molecule substances such as the patient's plasma proteins and large-molecule hepatocyte synthetic products may be prevented from returning to the patient. However, these proteins and coagulation factors can be administered separately by intravenous infusion. The accumulating large molecule concentration in the bioreactor can be monitored and controlled by replacement of the bioreactor fluid. The circuit through the dialysis cartridge can be used continuously or intermittently.

For even further safety, a third dialysis cartridge 37 can be added to the circuit, as shown in Figure 3. Here modulated filtrate emerges in the extra-fibre compartment of the dialysis cartridge 34 having passed through the pores of the semi-permeable membrane hollow fibres. The filtrate passes to dialysis cartridge 37 along line 36, passing through the semi-permeable membrane before continuing to dialysis cartridge 5 via line 38. The third cartridge 37 acts as a safety filter for large molecule toxic metabolites, cell debris and infective agents in case of fibre rupture in cartridge 34.

Blood Filtrate or Plasma Biomodulation

In the arrangement shown in Figure 4 blood from the patient circulates through a dialysis cartridge 5. Blood filtrate or plasma is pumped from the dialysis cartridge to the bioreactor. Detoxified filtrate or plasma containing hepatocyte-synthesised molecules returns to the patient along return line 23 and 30, the return line being guarded by an in-line millipore bacterial filter 39.

A similar arrangement is shown in Figure 5 in which blood circulates through an apherisis system 40.

In Figure 6, the system of Figure 4 is enhanced by returning the detoxified filtrate from the bioreactor through the hollow fibres of a subsidiary dialysis cartridge 34 from which it recirculates to the bioreactor allowing continued detoxification of metabolites in the bioreactor. Filtrate from the secondary circuit returns to the patient.

Although the invention has been described with reference to several embodiments, it should be appreciated that it may be embodied in many other ways. For instance, the hepatocytes may be of human or animal origin or animal or human hepatocyte-derived cell lines. The polyester matrix within the bioreactor may comprise other forms as well as the discs described. The hepatocytes in the bioreactor may be bathed in plasma, serum, blood filtrate or other fluid which circulates from the bioreactor and exchanges with the blood of the patient. A charcoal filter may be included on the outflow line from the dialysis cartridge or apherisis system to the bioreactor.

It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the invention as shown in the specific embodiments without departing from the spirit or scope of the invention as broadly described. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

CLAIMS:

1. An artificial liver support system, including:

a bioreactor in which hepatocytes are maintained in culture; an exchange barrier having two sides; a first circuit which is arranged to carry fluid from the bioreactor to a first side of the exchange barrier and back; and a second circuit which is arranged to carry blood from a patient to the second side of the exchange barrier and back.

2. An artificial liver support system according to claim 1, wherein the bioreactor has an associated computerised control system.

3. An artificial liver support system according to claim 2, wherein the bioreactor includes a containment vessel maintained at constant temperature in a water bath or otherwise, and a temperature probe reports the temperature of the bioartificial containment vessel to the computer system to allow feedback control of its temperature.

4. An artificial liver support system according to claim 2 or 3, wherein a gas exchanger receives fluid from the bioreactor, and injects oxygen, carbon dioxide, nitrogen or air in doses measured by computer system, and a dissolved oxygen probe provides a measure of dissolved oxygen to the computer system to allow feedback control of the gases.

5. An artificial liver support system according to claim 2, wherein a pH probe provides a measure of pH to the computer system to allow feedback control of pH.

6. An artificial liver support system according to any preceding claim, wherein within the bioreactor vessel, animal or human hepatocytes or animal or human hepatocyte-derived cell lines are carried in a suitable matrix and bathed in plasma, serum, blood filtrate or other suitable fluid.

7. An artificial liver support system according to any preceding claim, wherein fluid from the bioreactor is pumped through the first circuit to circulate in one direction through the extra-fibre compartment of a first dialysis cartridge, and is then returned to the bioreactor, and blood passes or is pumped through the second circuit from the patient in the reverse direction through the hollow fibres of the dialysis cartridge, and is then returned to the patient.

8. An artificial liver support system according to claim 7, wherein detoxified fluid from the bioreactor is directed through a second dialysis cartridge and filtrate from the second cartridge passes to the first cartridge.

9. An artificial liver support system according to claim 8, wherein the semi-permeable membrane pore sizes of the second cartridge are smaller than those of the first cartridge.

10. An artificial liver support system according to claim 7, 8 or 9, wherein plasma proteins and coagulation factors are administered by intravenous infusion.

11. An artificial liver support system according to claim 8, 9 or 10, wherein a third dialysis cartridge is added to receive the modulated filtrate emerging from the second cartridge and filter it again before passing it to the first cartridge.

12. An artificial liver support system according to any one of claims 1 to 6, wherein blood from the patient circulates through a dialysis cartridge or an apherisis system, blood filtrate or plasma is pumped from the dialysis cartridge, or apherisis system, to the bioreactor, and detoxified filtrate or plasma containing hepatocyte-synthesised molecules is returned to the patient traversing an in-line millipore bacterial filter.

13. An artificial liver support system according to claim 12, wherein the detoxified filtrate is returned from the bioreactor through a subsidiary dialysis cartridge.

14. An artificial liver support system according to any preceding claim, wherein a charcoal filter is included on the outflow line from the dialysis cartridge or apherisis system to the bioreactor.

15. A method of processing blood, including the steps of:

maintaining hepatocytes or hepatocyte-derived cell lines in culture in a bioreactor;

carrying fluid from the bioreactor to the first side of an exchange barrier having two sides, and back to the bioreactor;

carrying blood from a patient to the second side of the exchange barrier and back to the patient;

transporting the constituents of the patient's blood which have increased concentration, when compared to the levels in the fluid circulated through the bioreactor, and which include fulminant hepatic failure toxic metabolites, from the patient's blood through the exchange barrier; and

metabolising the toxic fulminant hepatic failure metabolites in the bioreactor.

transporting hepatocyte-synthesised substances from the bioreactor fluid to the patient.

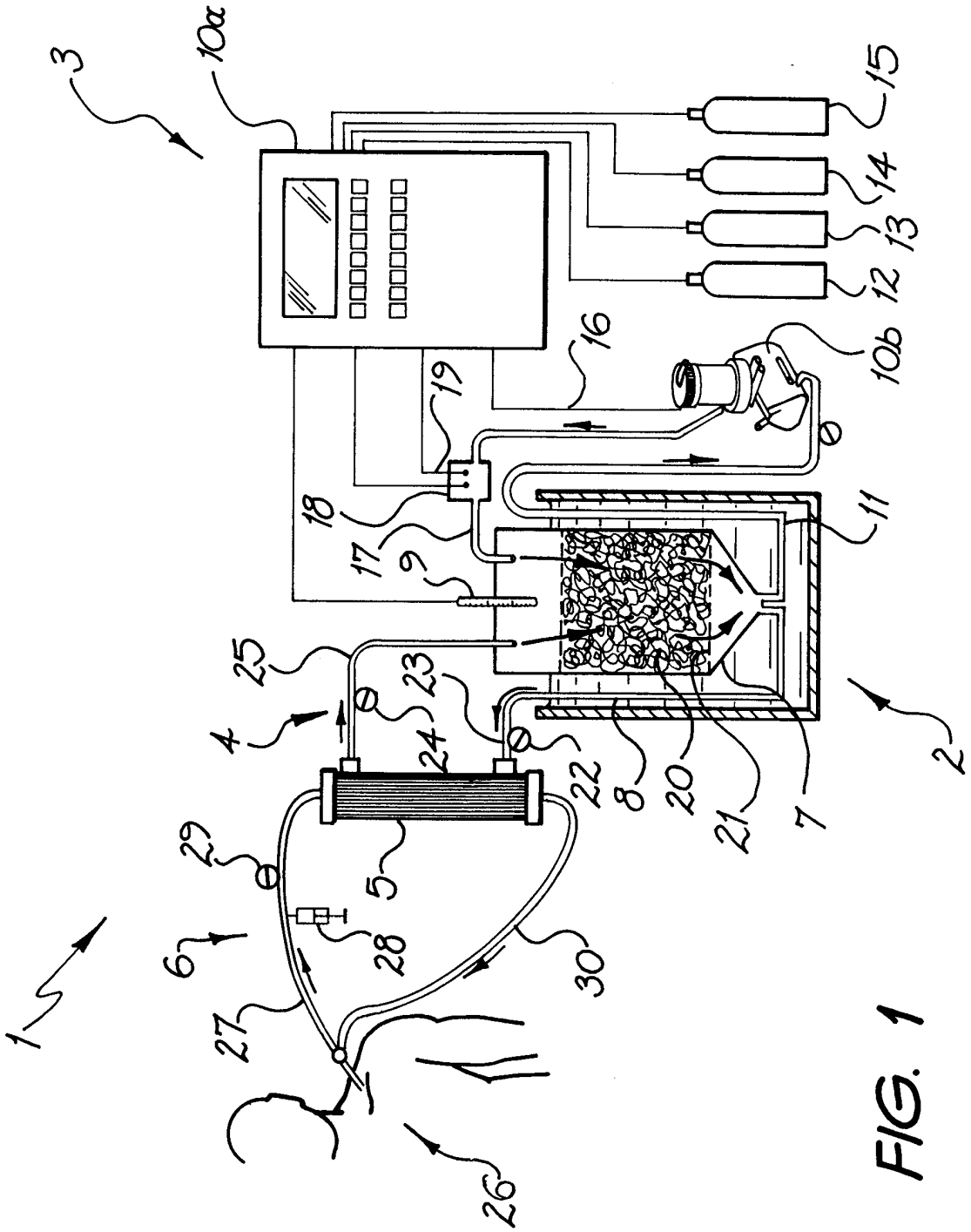
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FIG. 1

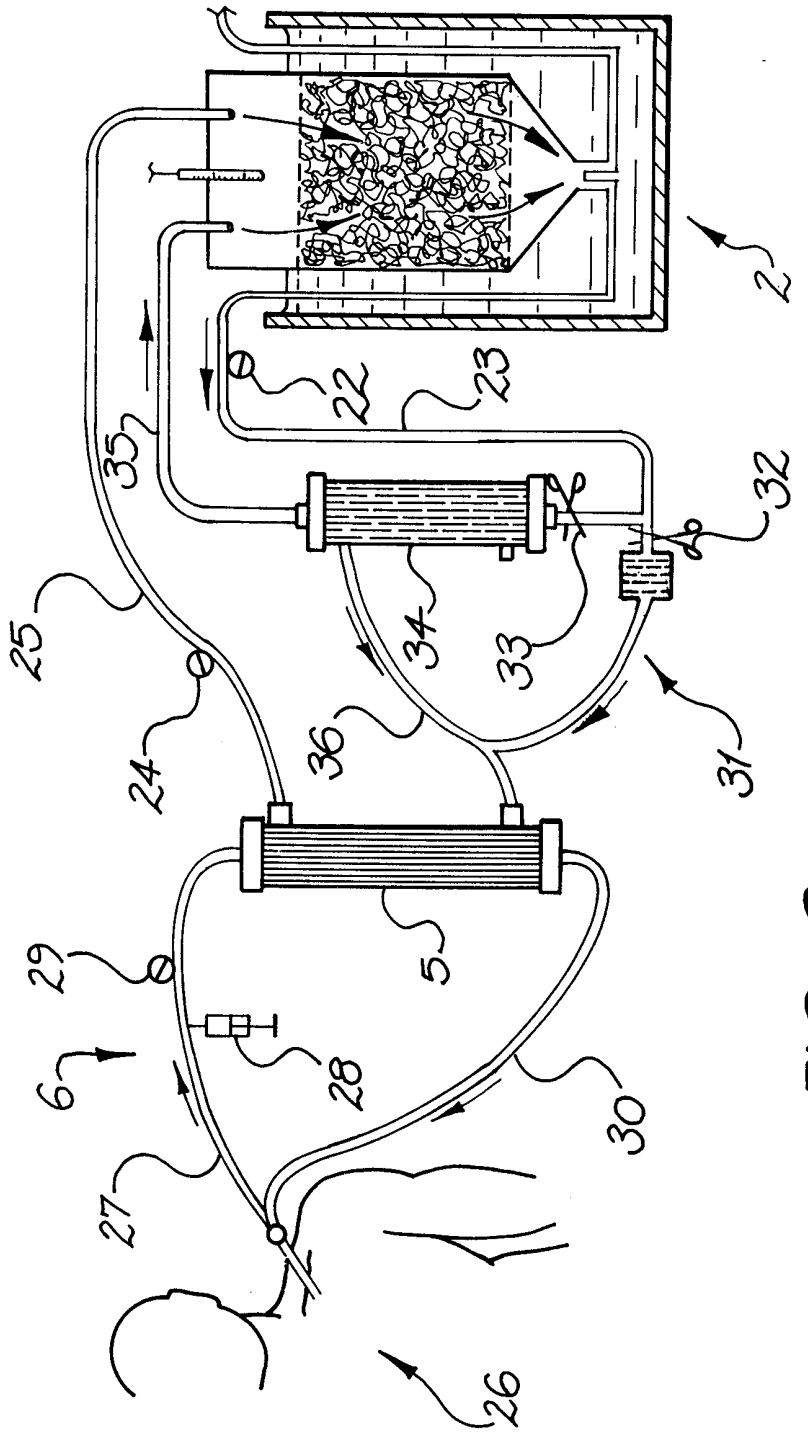

FIG. 2

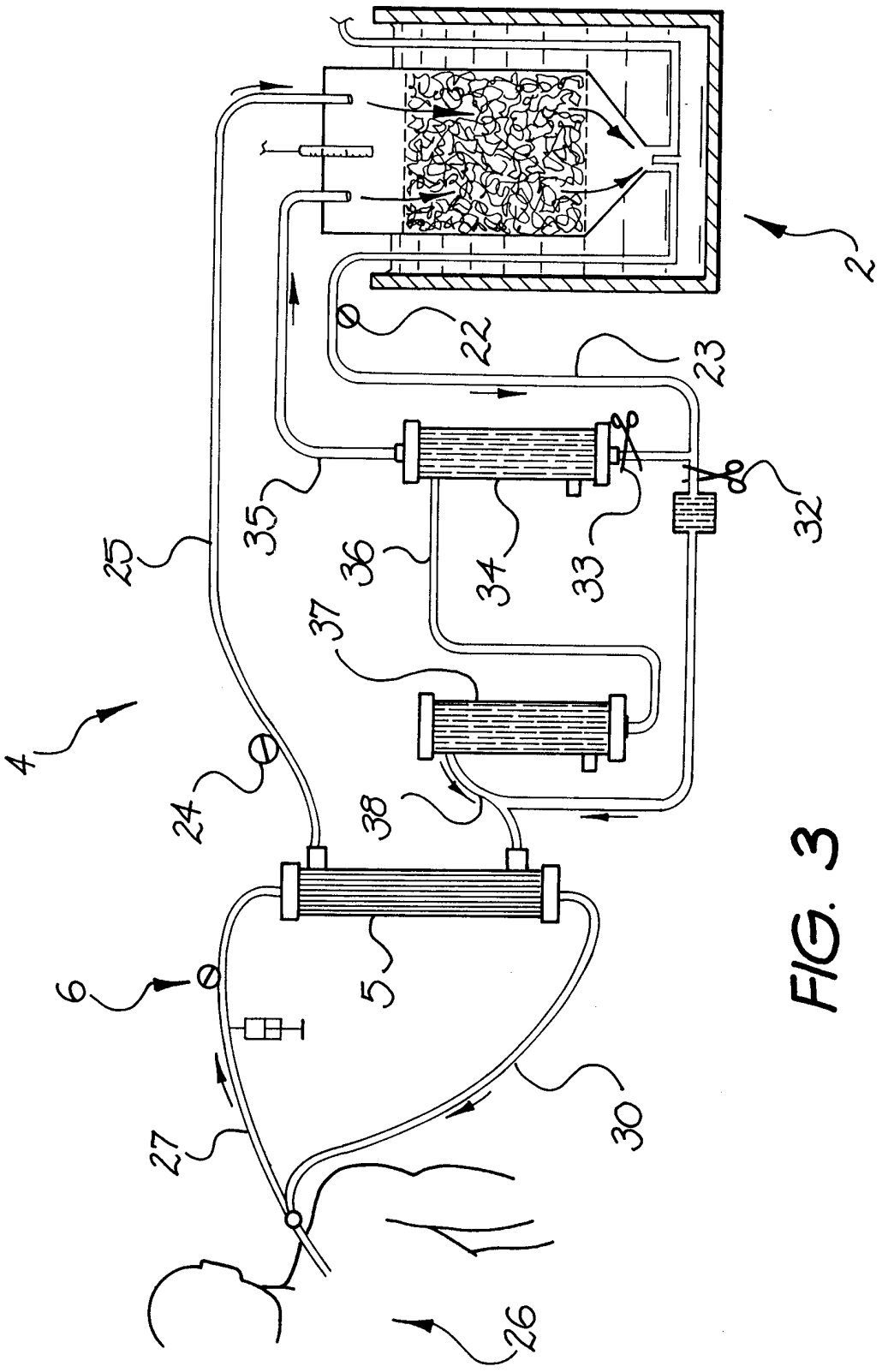

FIG. 3

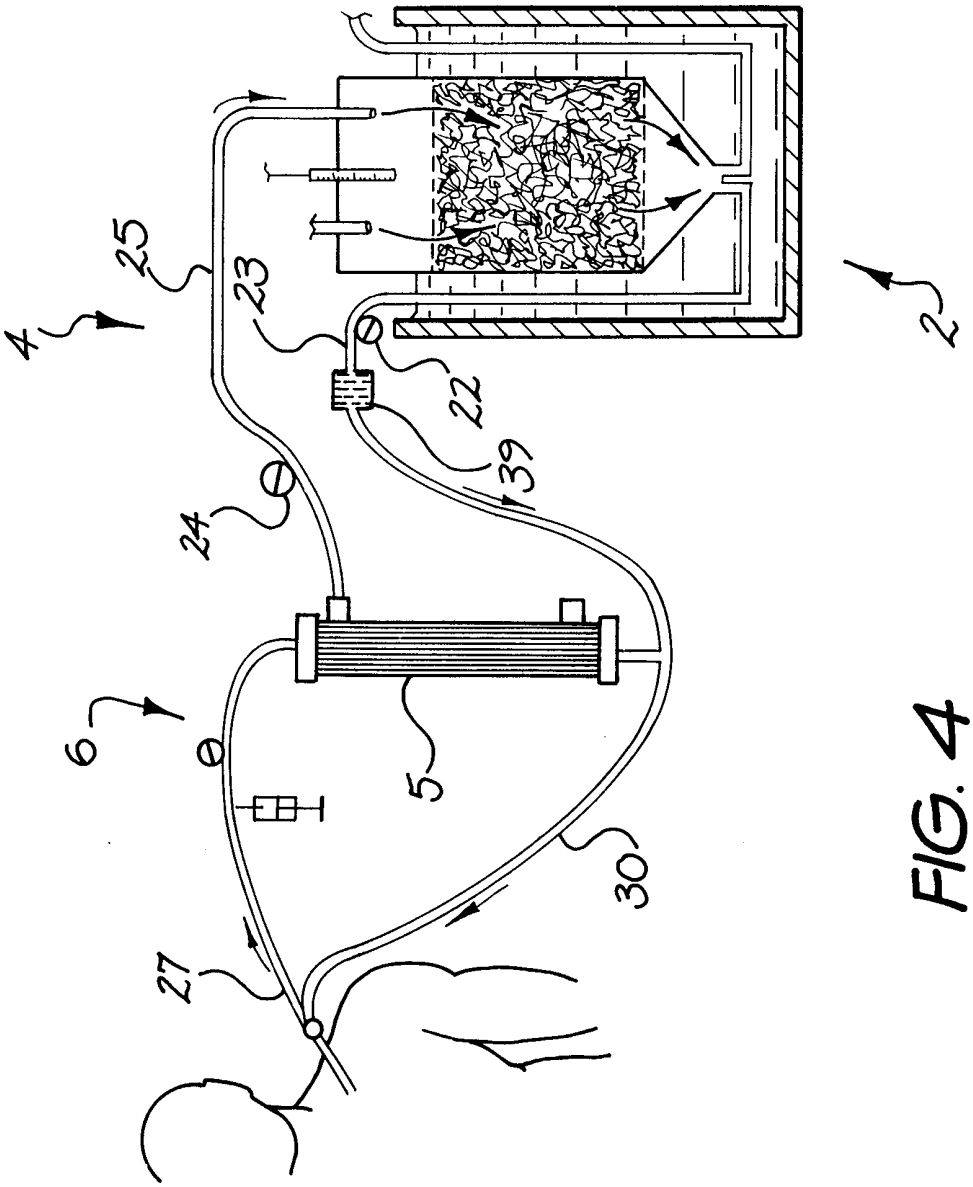

FIG. 4

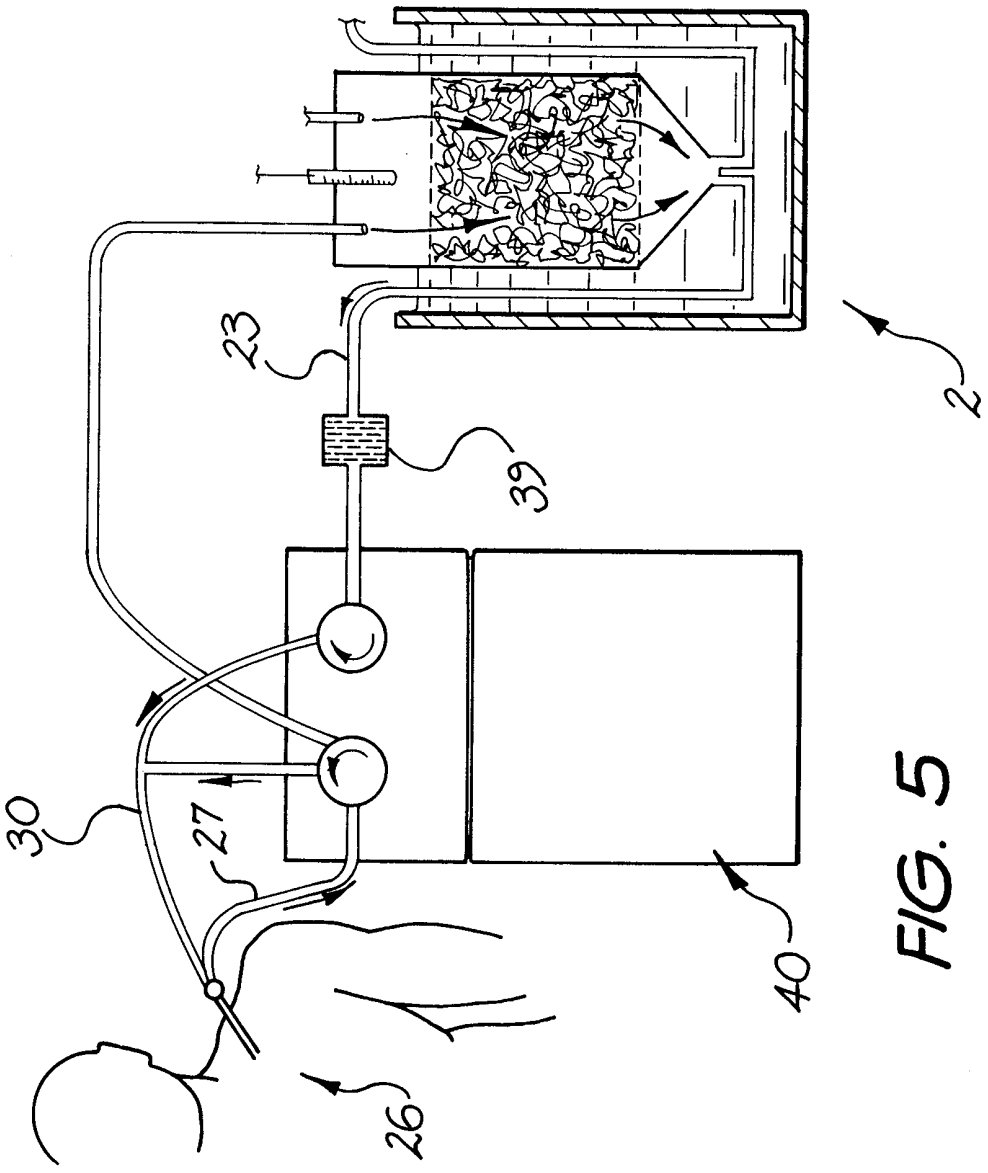

FIG. 5

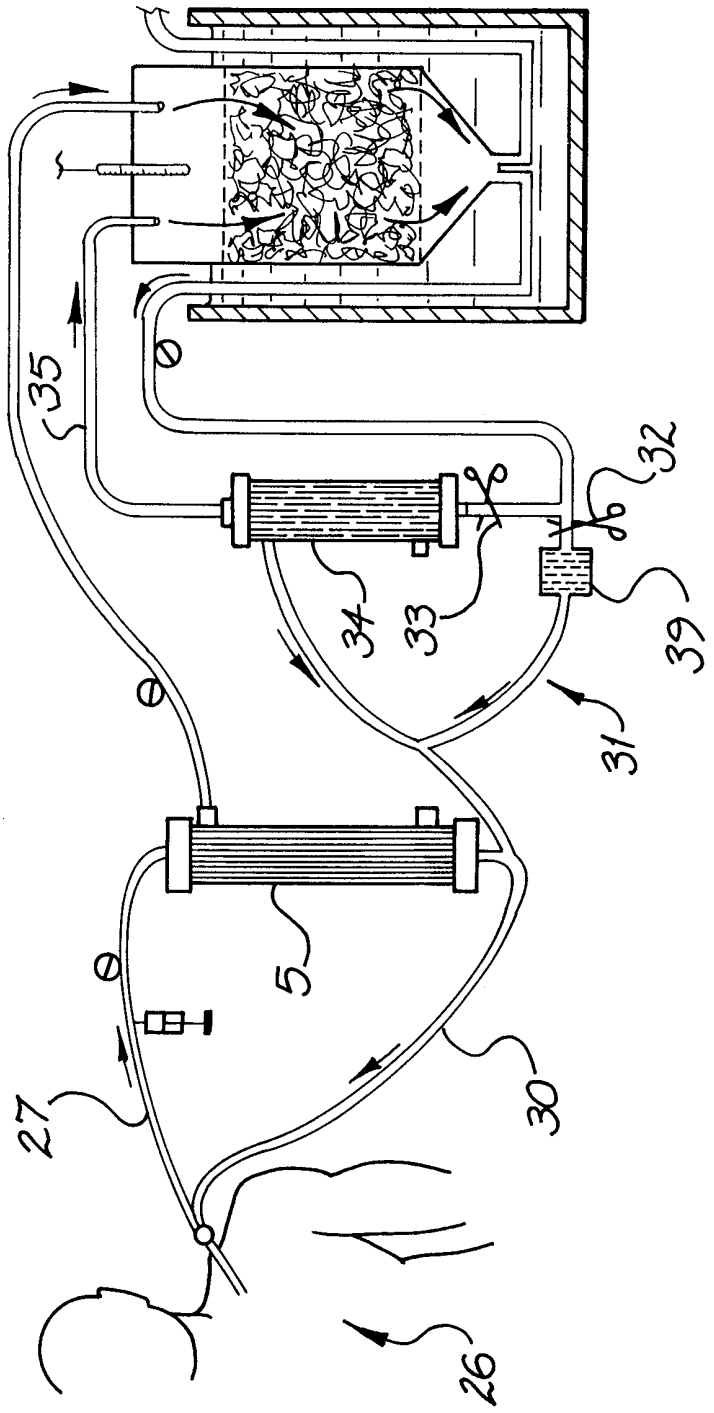

FIG. 6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 98/01065

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[6]: A61M 1/34; B01D 61/28

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)
IPC: A61M 1/-; B01D 61/-

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
IPC AU: A61M 1/34, 1/16; B01D 61/28

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WPAT & JAPIO + Keywords (HEPA:, LIVER:, BLOOD:, CELL:, CULTURE#,)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96/09876 A1 (XENOGENEX, INC) 4 April 1996 Figure 1	
A	WO 93/16171 A1 (MONSANTO COMPANY) 19 August 1993 Figure 3	
A	US 5328614 A (MATSUMURA) 12 July 1994 Figure 5	

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☒ See patent family annex

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Date of the actual completion of the international search	Date of mailing of the international search report
27 January 1999	-4 FEB 1999
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No.: (02) 6285 3929	Authorized officer **GEOFF SADLIER** Telephone No.: (02) 6283 2114

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International application No.
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This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
WO	96/09876	EP	784499	CA	2201159	CN	1127995
		AU	79594/94				
WO	93/16171	AU	34373/93	EP	579804	MX	9300674
US	5328614	US	5078885	WO	96/01680		

END OF ANNEX