

A PORTABLE APPARATUS FOR TRANSPORT OF BIOLOGICAL SAMPLES

TECHNICAL FIELD

[0001] The present invention relates to a portable apparatus for transport of biological samples, in particular for transport of human organs and tissues.

5 BACKGROUND ART

[0002] The following discussion of the background art is intended to facilitate an understanding of the present invention only. The discussion is not an acknowledgement or admission that any of the material referred to is or was part of the common general knowledge as at the priority date of the application.

10 [0003] Optimal organ preservation and transportation is critical to the survival of transplant patients with a range of medical conditions including, for example, lung, heart, liver or kidney diseases. A more or less comprehensive list of organs would include heart, lung, kidney, liver, pancreas and intestines. Tissues – such as bone, tendon, heart valves, corneas, skin, limbs or digits – may also require transport.

15 [0004] Organ donation typically requires the transport of organs from the site of the donor to the site of the recipient. This must be done in a manner that is sterile and preserves the viability of the organ for the duration of transport, which may last a number of hours. Failure to meet these conditions is likely to lead to adverse health outcomes for the transplant recipient. While organ donation is referred to above,
20 the same considerations apply to tissues for transplantation, and biological samples for human and animal use – for example blood products, vaccines and biologic agents.

[0005] Conventional organ transportation involves immersing an organ in cold preservation fluid, then packaging in three sequential plastic bags. The packaged
25 organ is then buried in crushed frozen saline and ice in a cooler (i.e. “picnic cooler” storage). This ‘static cold storage’ approach relies on using ice as a phase change material to cool the organ, thereby preserving it by reducing its metabolic rate. However, this approach poses several issues. Firstly, in conventional practice, there is no mechanism by which temperature is monitored or controlled within the cooler.
30 Given that the freezing temperature of ice is 0°C and that of frozen saline is around

-0.5°C, the organ is subject to subzero conditions, which is far below the accepted standard of 4-8°C for optimal organ preservation and leads to hypothermic injury. Secondly, this cooling mechanism relies on the rate and the uniformity of ice melting around the organ, which is unlikely to be even or precise. This leads to heterogeneity of metabolism within the organ and compromises its overall viability. Thirdly, turbulence coupled with the weight of litres of crushed ice during transport causes pressure injury and mechanical stress. Lastly, once the organ reaches the recipient site, it is rapidly warmed to body temperature at 37°C, causing a cascade of inflammatory events called rewarming injury, which results in further cell injury and cell death. These collectively contribute to poorer donor organ viability and poorer transplant recipient outcomes.

[0006] Cooling systems using phase change materials (PCMs), as described in *US20220154992A1* and *US8927257B2*, continue to rely on passive heat transfer, which can maintain stable temperatures but lack precision, control and speed. These systems achieve improved temperature conditions compared to conventional practice by using PCMs with melting temperatures within 4-8°C, thereby preventing hypothermic injuries. However, being a fixed mass with fixed physical properties, PCMs are unable to adjust for external temperature conditions or the individual mass of the organs. Furthermore, the cooling rate of the PCMs is limited by its physical properties and its cooling capacity is highly dependent upon the preconditioning practices of individual institutions, leading to variabilities of its efficacy. The Applicant's bench top experiments and modelling, as indicated in Figs. 16 and 17, showed that the time to reach target temperature using PCM technology was as long as 1.5 hours, which is significant as it is a over a quarter of the total recommended ischaemic time in the transportation of a donor heart.

[0007] Perfusion machines, such as those described in *US7572622B2* and *US9301519B2*, provide continuous circulation of preservation fluids, blood products and dissolved oxygen to improve organ viability during transport. However, these machines are large, complex and expensive. Their limited portability makes these machines impractical for the transport of organs between sites, particularly over long distances. Furthermore, large randomised controlled trials have not demonstrated a significant benefit for perfusion machines over conventional practice, except in the context of extended criteria donor organs (ie. Donor organs that would traditionally not be used in transplantation).

[0008] Currently, there is no portable solution on the market that is capable of providing a comprehensive system that can achieve rapid cooling of organs to the desired temperature in less than 60 minutes, prevent overcooling and hypothermic injury, enable controlled rewarming prior to transplantation, actively adapt to variations in temperature conditions externally and organ conditions internally, and protect organs against mechanical stress during transportation. The absence of such a system creates a critical gap in the market in organ preservation and transportation, as existing technologies fail to address these issues simultaneously.

[0009] The above discussion of the background art is intended to facilitate an understanding of the present invention. Although the above discussion relates to organs, it will be understood that similar issues may be applicable to other tissues and biological samples.

[0010] It is an object of the present invention to overcome or ameliorate at least one or more of the disadvantages of the prior art.

15 SUMMARY OF INVENTION

[0011] With this object in view, a first aspect provides a portable device for transporting a biological sample comprising:

- (a) a housing accommodating a storage chamber for receiving the biological sample;
- (b) a thermoregulation system for adjusting the temperature of the storage chamber, said thermoregulation system comprising:
 - a heat exchange system for transferring heat between the biological sample and the storage chamber;
 - a temperature monitoring system for sensing the temperature of the storage chamber and the biological sample; and
 - a controller for active control of the heat exchange system dependent on the input from the temperature monitoring system,

wherein the controller operates the heat exchange system to adjust the storage chamber temperature according to a selected temperature control program. This active control allows for more precise temperature management than prior technology, which is solely reliant on passive heat exchange, and allows easy adaptation for different use cases.

5 [0012] Desirably the heat exchange system includes a heating module to enable a controlled increase in temperature. Such a heating module may enable gentle rewarming of the organ to mitigate the risk of rewarming injury and help to prevent overcooling in cold external conditions, as encountered in airplane cargos and cold climates.

10 [0013] Preferably, the temperature control program is integrated with the thermoregulation system, such that temperature settings can be adapted to the requirements of the biological sample. For example, different organs have different cellular compositions and metabolic requirements, and may benefit from different temperature settings and temperature control programmes. Advantageously, the
15 controller may be configured with a plurality of temperature control programs allowing the portable device to be adapted to the transportation of a wide range of biological samples, including organs, tissues or other biological materials.

20 [0014] The selected temperature control program conveniently controls the heat exchange system to adjust temperature of the storage chamber and biological sample within a selected temperature range, for example 4-8°C for organs. The temperature control program preferably allows a controlled rate of temperature adjustment, for example for cooling which is significantly faster than cooling using a PCM. Similar requirement for controlled temperature adjustment may apply to heating. At the same time, unlike a PCM, the controller may advantageously
25 prevent overshoot of a lower temperature limit. The selected programs may have upper and lower temperature limits. It engages the thermoregulation system to provide heating if the sensed temperature is below the lower temperature limit, or if the rate of cooling is too fast, and provide cooling if the sensed temperature is above the upper temperature limit.

30 [0015] Preferably, the portable device further comprises a circulation module for pumping a circulation fluid through the heat exchange system for regulating the temperature of the biological sample when received in the storage chamber. This facilitates heat transfer in both cooling or rewarming modes and provides more

precision in the control of temperature of the biological sample. The circulation fluid may be used in two different contexts: non-contact with the biological sample or in direct contact with the biological sample. The non-contact circulation fluid may be a heat exchange fluid such as a refrigerant or PCM that is optimised for thermal efficiency rather than biocompatibility with the biological sample. For a circulation fluid in direct contact with the biological sample, examples may include organ and tissue preservation fluids such as the University of Wisconsin solution, or isotonic solutions such as a normal saline solution. The integration of the circulation module with the thermoregulation system further facilitates the precision of temperature control, the efficiency of heat exchange and the speed of temperature regulation.

[0016] A preferred embodiment comprises at least one tissue protection module, which is designed to protect the biological sample from mechanical stress and injury. The tissue protection module desirably provides a cushion that may comprise a heat conductive material in the form of a gel, a gas, a liquid, a foam or a semi-solid. The tissue protection module may conveniently line the inside of the storage chamber and surround or enclose the biological sample.

[0017] Returning to the circulation module described above, in one embodiment of the invention, a circulation fluid may be pumped through the tissue protection module. The circulation fluid can, as described above, be circulated through as a contact circulation fluid or non-contact circulation fluid depending on the design of the tissue protection module and whether or not contact with circulation fluid is desirable for the particular biological sample, in particular organ or tissue. For example, continuous contact with circulation fluid may be desirable for a heart or a kidney, but undesirable for an amputated digit which can suffer from maceration following prolonged exposure to fluid.

[0018] The tissue protection module may optionally be integrated with the heating module, being provided, for example, resistive heating or Peltier heating elements.

[0019] The biological sample, particularly organs and tissues, should be packaged in a sterile packaging system, typically including a plurality of bags. The packaging system is desirably integrated with the temperature monitoring system to allow accurate measurement of temperature of the biological sample. The packaging system may also be connected to the circulation module in a manner that allows circulation fluid to flow around the biological specimen to maximise heat transfer and

temperature control. In this embodiment, the shape of the bag(s) may be tailored to the shape and sizes of different organs and tissues to reduce turbulent flow, which further enhances heat transfer.

5 [0020] Similar to the tissue protection module, the packaging system may also comprise heating element(s) to enable rewarming of a biological sample. The heating element may be operable through connection, by an electrical connector, to an energy source for the portable device even when the packaging system is removed from the portable device. Where the packaging system is disposable, the electrical connector may be disconnected from the energy source to enable
10 disposal.

[0021] The tissue protection module and the packaging system can both be removed from the external housing and folded to allow convenient transport as flat packs

15 [0022] The thermoregulation systems for the portable device may comprise any practical combination of heating and cooling modules that allow active temperature control. The thermoregulation system may include heat exchange systems such as an absorption refrigeration system, a PCM system, a resistive heating system and a Peltier system for both heating and cooling. A PCM, particularly in combination with the circulation module, may be preferred for cooling.

20 [0023] Desirably, the portable device is designed to enable safe temperature management of the biological sample even in the event of a fault. In the event of a fault with the thermoregulation system such that a specific temperature control program could not be delivered, an electronic back up could be engaged both automatically and manually according to a fault mitigation strategy, to deliver a set
25 safe constant temperature. In the event of a fault with the entire thermoregulation system or the temperature monitoring system, another fault mitigation strategy could be deployed manually. For example, an endothermic chemical reaction or a back up PCM could be activated by the user to achieve a set safe constant temperature.

30 [0024] In a second aspect, there is provided a method for controlling temperature of a biological sample comprising:

- (a) receiving the biological sample in a storage chamber of a portable device;

- 7 -

- (b) adjusting temperature of the storage chamber with a thermoregulation system comprising a heat exchange system for exchanging heat between the biological sample and the storage chamber;
- (c) sensing the temperature of the storage chamber and the biological sample; and
- (d) actively controlling the operation of the heat exchange system dependent on the sensed temperature,

wherein the heat exchange system is controlled according to a selected temperature control program.

[0025] The temperature control program may be selected dependent on the nature of the biological sample as described above. A rewarming temperature control program allows rewarming of the biological sample to mitigate rewarming injury, for example in the context of an organ transplant.

[0026] The portable device for transport of biological samples may be applied to a range of biological samples, from organs to vaccines, with precise temperature control in either cooling or rewarming modes according to appropriately programmed temperature control strategies. At the same time, such biological samples may be protected by a combination of packaging system and tissue protection module, which provides protection from mechanical stress and injury while also enhancing accurate temperature control, particularly when integrated with the circulation module and the circulation fluid in direct contact with the biological sample.

BRIEF DESCRIPTION OF THE DRAWINGS

[0027] Further features of the present invention are more fully described in the following description of several non-limiting embodiments thereof. This description is included solely for the purposes of exemplifying the present invention. It should not be understood as a restriction on the broad summary, disclosure or description of the invention as set out above. The description will be made with reference to the accompanying drawings in which:

[0028] Figure 1 a schematic orthogonal view of the portable device for transport of biological samples according to a first embodiment.

[0029] Figure 2 is a schematic cross-sectional view of the portable device of Figure 1.

5 [0030] Figure 3 is a schematic cross-sectional view of a portable device for the transport of biological samples, comprising a heating and a cooling module in a second embodiment.

[0031] Figure 4 is a schematic cross-sectional view of a third embodiment of a portable device for transport of biological samples comprising a circulation module.

10 [0032] Figure 5 is a schematic cross-sectional view of a fourth embodiment of a portable device for transport of biological samples comprising a circulation module.

[0033] Figure 6 is an orthogonal exploded view of a portable device for tissue transport of a fifth embodiment comprising a tissue protection module featuring temperature sensors of a temperature monitoring system.

15 [0034] Figure 7 is an exploded view of a portable device for transport of biological samples, according to a sixth embodiment. This embodiment features a circulation module which utilises peristaltic pumps to pump cooled or warmed non-contact circulation fluid or gel into a tissue protection module.

20 [0035] Figure 8 is a schematic exploded view of the portable device for transport of biological samples. This embodiment features a circulation module which utilises peristaltic pumps to pump cooled or warmed contact circulation fluid into a packaging system housing an organ or tissue.

25 [0036] Figure 9 is a front view of a packaging system for an organ such as a heart according to an embodiment comprising inlet and outlet tubes which connect to a circulation module and locally heated bonded sections or "leaf-seals" of the package designed to suspend the organ in the packaging system to allow circulation fluid to flow through and evenly around, including below the organ.

[0037] Figure 10 is a first orthogonal view of the packaging system of Figure 9.

- [0038] Figure 11 is an orthogonal view of an alternative packaging system, which features temperature sensors mounted on the surface, but does not feature inlet and outlet tubing.
- 5 [0039] Figure 12 is a schematic exploded view that shows a foldable tissue protection module for the packaging system for a heart as shown in Figure 11.
- [0040] Figure 13 shows an orthogonal view of the foldable tissue protection module of Figure 12 and the packaging system of Figure 11 in active use.
- [0041] Figure 14 shows the foldable tissue protection module of Figure 13 in unfolded condition.
- 10 [0042] Figure 15 is an exploded view of a portable device for tissue transport according to a ninth embodiment comprising a compressor-based refrigeration .
- [0043] Figure 16(a) shows a schematic of a cooling system for the current clinical standard of care applying to organ (heart) transplant.
- 15 [0044] Figure 16(b) shows a modelled temperature time profile (0 to 26 Hours) for the components of the cooling system and the organ and Figure 16(c) shows a detail from Figure 16(b) with emphasis on the first 10 hours.
- [0045] Figure 17 shows experimental setup and results in the form of a temperature time profile for cooling a test sample with a -5°C phase change material.
- 20 [0046] Figure 18 shows experimental setup and results in the form of a temperature time profile for cooling a test sample contained in a sealed bag with a -25°C phase change material.
- [0047] Figure 19 shows experimental setup and results in the form of a temperature time profile for cooling a test sample contained in a packaging module
- 25 which is cooled through pumping contact circulation fluid from a cold reservoir.

DESCRIPTION OF PREFERRED EMBODIMENTS

[0048] Referring to Figures 1 to 8, there is shown a portable device 10 for transport of a biological sample under precise temperature control according to a number of

embodiments. In all embodiments, device 10 has cooling and heating functionality as described later.

5 [0049] By “biological sample” is intended – without limitation – any tissue or organ, for example heart, lung, liver, kidney, intestine, pancreas. Also included within the definition is an amputated digit, amputated limb or cornea. Biologicals are also not limited to blood products, laboratory samples vaccines or medicaments. “Tissue” and “organ” are used interchangeably, for the purpose of example only, in the following description.

10 [0050] By “thermoregulation system” is intended a system that actively controls temperature of a biological sample, when received within portable device 10, by controlling the operation of a heat exchange system for exchanging heat – whether for cooling or heating –

15 for example allowing rewarming of a biological sample – between the biological sample and the storage chamber by a heat exchange system, on the basis of the temperature detected by the temperature monitoring system. The heat exchange system may be of any suitable type, for example being a refrigeration system of compressor or absorption type, a Peltier cooling system or a PCM and so on. In some embodiments, a circulation module is desirably included to pump a circulation fluid, conveniently a liquid or low viscosity gel, to allow efficient heat transfer
20 between the biological sample and heat exchange system, and precise temperature control. The circulation fluid may directly contact the biological sample and comprise of, these not intended to be limiting, a preservation fluid or isotonic solution that is compatible with the biological sample. Alternatively, the circulation fluid may be non-contact with the biological sample, in which case, the circulation fluid may
25 be a refrigerant, antifreeze, cryopreservative or PCM, phase change material, these not intended to be limiting. As the biological sample is received in a storage chamber of portable device 10, the terms “biological sample temperature” and “storage chamber temperature” may be used interchangeably in the following description. The thermoregulation system may also have back up mode(s) that
30 allow safe operation of portable device 10 when a fault is detected.

[0051] The term “tissue protection module” is defined as any apparatus for mechanical protection of the biological sample. Desirably, the tissue protection

- 11 -

module is configured to aid heat transfer and, to this end, the circulation fluid may flow through the tissue protection module as described in embodiments below.

5 [0052] Device 10 has a body 11 which forms the outer case of the device 10. Body 11 is designed to contain the systems, modules and other components of the device 10 as described below.

10 [0053] In one embodiment, the body 11 comprises a hard outer shell to protect the internals of the portable device 10 as well as tissue stored within it. Preferably, body 11 is of a substantially waterproof or water-resistant material. A suitable material for body 11 may be selected from plastics, metals or alloys. The material may, for example, be selected from the group consisting of acrylonitrile butadiene styrene (ABS), polycarbonate and stainless steel. Other desirable properties of the material of body 11 include strength, dent/scratch resistance, corrosion resistance and light weight. The material of body 11 is also desirably non-porous with 'easy to clean' surfaces. Cleaning of the reusable components of this invention is, in all
15 embodiments, by wiping down with hospital grade disinfectants. Body 11 may be provided with wheels 29 for mobility.

20 [0054] The dimensions and volume of body 11 may be selected according to its purpose. The following volumes are examples only and are not intended to be limiting in any way with volume selection at manufacturer discretion. A small sized body 11 may have a volume of about 10 litres and be used for transport of donor tissues, eyes or amputated digits. A medium sized body 11 may have a volume of about 45 litres and be used for transport of donor hearts and certain donor organs – e.g. pancreas, kidneys – as well as amputated limbs and larger volumes of tissue.
25 A large size body may have volume of about 85 litres and be used for donor lungs and livers as well as amputated limbs. The portable device 10 is intended to be used as a universal container with capability to transport a range of biological samples, by nature, shape and mass, not limited to tissues and organs.

30 [0055] Device 10 includes a storage chamber 27 for accommodating the organ as described further below. A thermoregulation system 30 is provided for adjusting temperature within storage chamber 27. In some preferred embodiments, thermoregulation system 30 integrates both cooling and heating functions as will be

described later. In the context of organs, the cooling function is typically required to bring the organ temperature from 37°C to a safe, hypothermic condition at 4 to 8°C range.

- 5 [0056] A heating function enables active warming in a controlled manner following a temperature control program as will be described later. A heating function also enables precise rewarming of a biological sample, in particular, an organ for transplant or blood product for transfusion, as will also be described in detail later.

[0057] Temperature control of the biological sample may also involve operation of a circulation module 40 to pump a fluid around the biological sample as will also be described in detail later. Such circulation module 40 assists with even heat transfer between the circulation fluid and the biological sample.

5 [0058] At the top of body 11 and closing storage chamber 27 is a lid 12. Removal or opening of lid 11 allows access to the storage chamber 27 and the heat exchange system 30. Lid 11 may be sealed tightly, preferably with a hermetic seal, to prevent leaks (of air, fluids or solids) or risk of damage to a biological sample from the exterior. Storage chamber 27 may be held at ambient pressure. There is no
10 requirement to control pressure as well as temperature as described throughout this description.

[0059] The lid 12 may be sealed or closed by the use of lockable clasps 12a, which may be fabricated from a material such as stainless steel. Lockable clasps 12a may utilise hinges 12b, conveniently having a selected opening angle of 0-110 degrees.
15 Hinges 12b are torque hinges of corrosion resistant material such as stainless steel.

[0060] Body 11 may comprise an insulating material layer 140 to provide insulation to slow heat transfer through the body 11 into storage chamber 27. The insulating material layers may be provided in the form of insulated housings. Such insulation also allows the storage chamber 27 to be maintained at desired temperature for a
20 longer periods. Suitable insulation may include, without limitation, extruded or expanded polystyrene, polyisocyanurate, polyurethane or other polymeric foams.

[0061] Referring to Figure 2, the biological sample – in this embodiment tissue – is contained within a packaging system 60. The packaging system 60 is described in further detail below but may comprise two, three or a plurality of bags. The bags
25 may be zip lock bags. Dependent on the tissue transported the packaging system 60 may comprise a bag containing preservative solution or a biocompatible isotonic solution.

[0062] Storage chamber 27 also contains a plurality of cushions 52 forming one embodiment of tissue protection module 50. Three cushions 52 lining storage
30 chamber 27 are shown by way of example only. The cushions 52 provide physical support to the tissue and prevent mechanical stress and pressure injuries. As described below, the tissue protection module 50 – particularly when integrated with

- 14 -

a circulation module 40 as described below – may be configured to assist in heat transfer evenly across the tissue.

5 [0063] Storage chamber 27 may be provided with a temperature sensor 82 forming part of a temperature monitoring system for providing an input to control, by electronic control unit 100, of heat exchange system 30 and/or circulation module 40 of embodiments as described below. Temperature sensor 82 is positioned to monitor the temperature of the storage chamber 27. Position of temperature sensor 82 is optimised to provide an accurate temperature reading for the tissue. Temperature monitoring system 80 need not be limited to a single temperature or
10 temperature sensing for the storage chamber 27. Temperature monitoring system 80 may comprise a plurality of temperature sensors in the form of an array, several separate sensors or individually. An array of temperature sensors may allow an average temperature to be recorded or temperature to be recorded at different positions within the device 10, in particular, in the thermoregulation system 30 and/or circulation module 40 of embodiments described below. Such temperature
15 monitoring provides a basis for active temperature control by electronic control unit 100 with a selected temperature control program according to preferred embodiments.

[0064] Device 10 is provided with a battery 14 to provide power to components including electronic control unit 100. Device 10 may also be connected to an
20 external power supply as described below.

[0065] Body 11 may be provided, on its base, with wheels or castors 29 to permit easy movement.

Heat Exchange System 30

25 [0066] Heat exchange system 30 may be implemented in a number of embodiments as described below.

[0067] In one embodiment, the heat exchange system 30 is implemented using a compressor-based refrigeration system as is familiar to the person skilled in the art of refrigeration. Such a compressor-based refrigeration system takes advantage of
30 a heat pump effect, by evaporating a refrigerant in a reduced pressure atmosphere to remove heat from an enclosure (here storage chamber 27) before condensation

of the refrigerant caused by compressor. This causes excess heat to be lost to the environment before the refrigeration cycle – which at least cools an organ stored in storage chamber 27 – repeats itself.

5 [0068] Such a compressor-based refrigeration system may use any suitable refrigerant of which a wide range are available. Examples of refrigerants which may be used include propane, isobutane and hydrofluorocarbons (where permitted) including chlorodifluoromethane, difluoromethane, difluoroethane, tetrafluoroethane and hydrofluoroolefins as well as hydrofluorocarbon blends. Puron (R 410A) is also an example of a suitable refrigerant.

10 [0069] Such a compressor-based refrigeration system may provide cooling directly to the tissue. Alternatively, the compressor-based refrigeration system may provide the refrigerant or heat transfer fluid to a circulation module 40 in contact with the biological sample. The circulation module 40 may pump the refrigerant, or another fluid in contact with the refrigerant around the biological sample to enable more
15 efficient cooling.

[0070] In a further and desirable embodiment, the compressor-based refrigeration system may provide heating, acting as a heating or 'warming module'. As is also understood in the refrigeration art, compressor-based refrigeration systems may be run to introduce heat from the environment into an enclosure, here storage chamber
20 27, by condensing the refrigerant at the enclosure boundary. This is termed 'reverse cycle' operation. The device 10, 11 of Figures 2 and 15 employ such a compressor-based refrigeration system 131 with a radiator consisting of metallic tubing 135 under the control of electronic control unit 100.

25 [0071] Operation of the compressor-based refrigeration system may be precisely controlled by the electronic control unit as described below, and according to a temperature control program specific to the biological sample.

[0072] In a further embodiment, circulation module 40 circulates the refrigerant, or another fluid in heat transfer contact with the refrigerant, about the biological sample to enable heating. The circulation module 40 may thus facilitate either heating or
30 cooling dependent on temperature sensed by a temperature monitoring system as described below making active temperature control of storage chamber 27 and the biological sample possible.

Phase Change Material (PCM)

[0073] In alternative embodiments, heat exchange system 30 includes a PCM to provide cooling (or heating) of storage chamber 27.

5 [0074] A PCM is a material that transitions from one form of matter to another, for example solid to liquid, by absorbing or releasing a sufficient amount of latent heat. Therefore, a PCM may be used for cooling and heating.

10 [0075] The simplest PCM is water. A simple mix of water/ice will maintain a stable temperature of 0°C as long as the ice remains (assuming the temperature of the environment is above 0°C). There are many PCMs available and their properties may be tuned to allow for a variety of temperature settings to be maintained. This may be done by varying their nature or composition or by controlling the pressure above the PCM.

15 [0076] In embodiments of the invention, a PCM may be used to directly cool the biological sample. Preferably, the PCM enables cooling of a circulation fluid that is pumped around the biological sample by the circulation module 40. As the PCM maintains a stable temperature, the ECU 100 can control the circulation module 40 to vary the amount of cooled circulation fluid in contact with the biological organ to precisely delivery a desired temperature, which can be above the transition point of the PCM.

20 [0077] In a case, where the PCM – for example ice/water – is used for cooling without circulation module 40, a stable temperature of around 0°C may be maintained in the storage chamber 27. However, circulation module 40 may be operable to maintain a temperature above 0°C, such as 4°C, 8°C, 12°C, or another temperature above the transition point of the PCM. As will be appreciated by a
25 person skilled in the art of PCMs, the same principle can be applied to any PCM allowing for a wide range of temperatures to be obtained.

30 [0078] In embodiments of the invention using a PCM, a stable temperature may be maintained for as long as the PCM has not fully transitioned to another form. In the case of ice/water mixture, ice may be obtained and added to a compartment forming part of heat exchange system 30 during use. This may allow cooling to be prolonged indefinitely. Conversely, an alternative PCM may be used to provide a different temperature condition.

- 17 -

[0079] While the above description of PCMs primarily discussed a solid to liquid transition, the same principle may be applied to a liquid to gas transition allowing the latent heat of vapourisation to be utilised.

5 [0080] In an alternative embodiment, a gas or liquid may be compressed above atmospheric pressure and the pressure released in a controlled manner. This pressure release would cause the gas or liquid to vapourise and absorb heat. This principle may be used to provide cooling in thermoregulation module 30. This principle also enables cooling of the circulation fluid.

Absorption Refrigeration

10 [0081] In another embodiment, the heat exchange system 30 may be implemented using absorption refrigeration. As understood by the person skilled in the art of absorption refrigeration, the principle allows for cooling of an enclosure, here storage chamber 27, using a heat source such as electrical heating or combustion to drive the refrigeration system with a selected refrigerant. Absorption refrigeration
15 would allow the cooling system to work in a remote setting where mains electricity is not available. This principle also enables cooling of a fluid circulated by a circulation module 40 about the biological sample.

Peltier Based Cooling

20 [0082] In a further embodiment, a Peltier based cooling system may be used for heat exchange system 30. Peltier based cooling also enables cooling of a fluid circulated by a circulation module 40 about the biological sample.

[0083] A Peltier based cooling system could also be used for heating. By reversing the flow of current through a Peltier cooler, it may be used to provide heat allowing a Peltier based heat exchange system 30 to provide both cooling and
25 heating. Such a system would also enable cooling or heating of a fluid circulated by a circulation module 40 about the biological sample.

[0084] Otherwise, any suitable cooling technology may be used to provide cooling to the storage chamber and biological sample.

Tissue Protection Module

5 [0085] The storage chamber 27, being located within body 11, provides substantial physical protection to a biological sample. However, injury to an organ during turbulent transportation could still occur so inclusion of a further tissue protection module 50 is a feature of preferred embodiments.

10 [0086] Such tissue protection module 50 may provide a cushion for the biological sample. In one embodiment, the tissue protection module 50 may accommodate the circulation module 40 in close proximity to the biological sample, allowing a non-contact circulating fluid to be pumped into the tissue protection module 50 to evenly heat or cool the biological sample. The tissue protection module 50 also advantageously provides a means for securely supporting the biological sample within it.

15 [0087] The tissue protection module 50 accommodates a packaging system 60 for the biological sample. The packaging system 60 is described later. In both the cases of tissue protection module 50 and packaging system 60, a temperature monitoring system as described herein is preferably included. In some embodiments, one or both of tissue protection module 50 and packaging system 50 are provided, as required, with inlet and outlet pumps – for example peristaltic pumps – to receive or deliver circulation fluid.

20 [0088] In one embodiment, as shown in Figs. 2 to 5, the tissue protection module 50 comprises gel cushion(s) 52 containing a gel of low viscosity, conveniently between 1000 and 2000 centipoise, which allows the gel to be pumped in a desired embodiment as described below. The gel is preferably heat conductive and preferably has a freezing point lower than water to prevent the formation of ice
25 crystals. The gel cushion 52 desirably surrounds the biological sample protecting it from mechanical stress and injury, as well as enabling even heat transfer during cooling and rewarming.

30 [0089] Desirably, the gel based cushion may include a means for active circulation of the gel. In this embodiment, the gel based cushion forms part of the circulation module 40 allowing the gel cushion to be easily cooled and warmed to the desired temperature range.

[0090] The tissue protection module 50 here may comprise an inlet tube and an outlet tube, as shown in Figures 7 and 8. The circulation fluid may be pumped into the tissue protection module 50, circulating through it, and then exiting via the outlet tube. The outlet tube conveniently communicates with the heat exchange system
5 30 which either heats or cools the circulation fluid and pumps the fluid back through tissue protection module 52 as previously described. The rate, quantity and distance of the fluid circulated between inlet tube and outlet tube and the tissue protection module 52 can be configured to minimise turbulent flow and maximise heat transfer.

10 [0091] Heating or cooling of the circulation fluid may depend on its temperature as sensed at a convenient position, for example, at the outlet tube 54.

[0092] The gel cushion(s) 52 may be removable from the storage chamber 27 and device 10.

15 [0093] The gel cushion(s) 52 may also include a heating module, as described below, to allow controlled warming. Such a heating module, for example comprising resistive heating element or Peltier heating element, would enable warming either within the device 10, outside the device 10 or both. For example, in the case of an organ for transplant, the gel cushion 52 may be removed from the device 10, and the heating module could be activated outside of the device 10 by the temperature
20 control programme set to warming mode. This would allow efficient warming without the effect of a cooling element such as a PCM housed within the device 10.

[0094] As alternatives to a low viscosity gel, as above described, an air-based cushioning or liquid cushioning system could be implemented. An air-based cushioning system may take the form of air-pillows, bubble wrap, foam or a blend of
25 these. A liquid cushioning system could take the form of a free liquid, or a liquid contained within impermeable bags, for example of the packaging system 60 as described below. Cushioning systems may also involve semi-solids or microbeads and could be configured to enable direct contact with the tissue.

30 [0095] A liquid based cushioning embodiment, similarly to the gel cushioning embodiment, may be combined with the circulation module 40 to move heat to biological sample more effectively. For example, the liquid may be heated or cooled,

as required, to allow for the liquid cushion to be cooled or warmed to a desired temperature more easily.

5 [0096] As with the gel cushion, liquid cushion 52 may comprise an inlet tube 53 and an outlet tube 54. The circulation fluid – whether or not a refrigerant – may be pumped into the liquid cushion 52, circulating through it, and then exiting via the outlet tube 54. Outlet tube 54 conveniently communicates with the heat exchange system 30 which either heats or cools the circulation fluid and pumps the fluid back through liquid cushion 52. Heating or cooling of circulation fluid may depend on its temperature as sensed at a convenient position, for example, at the outlet tube 54.

10 [0097] Air or liquid cushions could also include a heating element as described with reference to the gel cushion.

15 [0098] The tissue protection module 50 preferably comprises means for suspending the biological sample within the storage chamber 27. Packaging system 60 for the biological sample is suspended by a suspending means without touching the walls of the storage chamber 27 or any other wall of the device 10. This would provide the advantage of limiting conductive heat transfer through the walls of storage chamber 27 or the device 10 generally.

Warming Module

20 [0099] The heat exchange system 30 may enable warming module of the biological sample, in particular an organ, to physiological temperatures in a controlled manner, that is evenly or uniformly warming the organ. For organs, the warming process must be completed prior to the implantation of the tissue to maximise the chances of success in a transplant. At present, the standard of care is to simply flush the organ with a warm solution before implantation. Use of a warming module, with the benefit of controlled, gradual increase in temperature, offers a superior alternative to the standard of care.

25 [00100] In preferred embodiments, warming or heating functionality could be integrated with cooling within the heat exchange system 30 and, where included, the circulation module 40. Such embodiments are described above. However, a cushion as described above could also be provided with a separate heating element, for example a Peltier element or a resistive heating element, for this purpose. Other

embodiments could include separate cooling and heating modules to form the thermoregulation module 30.

5 [00101] Heating may be provided by combustion of a fuel which may be used to provide heating to the warming module. In an embodiment, this may be combined with absorption refrigeration in the cooling module. This would allow the device to be used in an environment lacking mains electricity and be effective in remote environments.

Circulation Module 40

10 [00102] As described above, the heat exchange system 30 may be integrated with a circulation module 40 configured with a system of pumps and tubing that pumps the circulation fluid around a biological sample to efficiently control its temperature. The circulating fluid could be the refrigerant or biocompatible solution such as a preservation solution.

15 [00103] A range of liquids may be used as the circulating fluid depending on the context: a non-contact or a contact circulation fluid in relation to the biological sample. The non-contact circulation fluids may be a heat exchange fluid, such as a refrigerant, cryopreservative or PCM. The choice of non-contact circulation liquids depends on its heat transfer capacity and ability to remain in the liquid form at 0°C or below with biocompatibility a lesser consideration. A circulation fluid in direct
20 contact with the biological sample may include organ and tissue preservation fluids such as the University of Wisconsin solution, or isotonic solutions such as a normal saline solution. The choice of contact circulation liquids are based on its compatibility with the biological sample being transported.

25 [00104] The circulation module 40 may be integrated with the packaging system 60 as described below. In such embodiments, the sterile circulation fluid in direct contact with the biological sample within the packaging system may be used to facilitate heat exchange. A convenient circulating fluid in direct contact with organs and tissues may include as the University of Wisconsin and normal saline solutions.

30 [00105] In embodiments, the circulation module 40 may include disposable tubing. As the circulation module 40 includes a pump, cushion, cushion connections (e.g. inlet tube and outlet tube as described above) and any other tubing forming portion of the circulation module 40 and heat exchange system 30, the pump may be

- 22 -

disconnected from the tubing. This would allow the tubing of device 10 to be disposed, enabling sterility of the system to be maintained after each use.

[00106] The flow of circulating fluid through the circulation module 40 may be controlled by pumps and valve(s).

5 [00107] A range of pump types may be suitable, including peristaltic pumps, syringe pumps, diaphragm pumps, gear pumps, centrifugal pumps, micropumps, rotary vane pumps, piston pumps, membrane pumps, needle pumps, infusion pumps, vacuum pumps, insulin pumps, elastomeric pumps, osmotic pumps, implantable pumps, positive displacement pumps, axial flow pumps, impeller pumps and rotary
10 lobe pumps. In some embodiments, a pump may be selected with to reduce turbulent flow. Peristaltic pumps may be preferred in some embodiments.

[00108] Conveniently, the pump is electrically operated under the control of an electronic control unit (ECU) 100 for portable device 10. The ECU is described below. Dependent on the temperature control program for the ECU, the pump and
15 circulation module 40 is operated in either cooling or warming mode, depending on whether the temperature detected is above or below the desired settings. In this manner, the circulation module 40, when combined or co-operating with the heat exchange system 30 and the ECU, form the thermoregulation system, which can deliver a range of temperature control programmes that may be specific to different
20 type of biological samples.

Temperature Monitoring System

[00109] Preferred embodiments of the device 10 include a temperature monitoring system for sensing temperature of storage chamber 27 and the biological sample.
25 Temperature monitoring may involve any suitable temperature sensor 82, for example a thermocouple, an infrared imaging system or a plurality of temperature sensing devices. A plurality of temperature sensors may be included.

[00110] The temperature monitoring system 80 provides temperature signals which are inputs for the control of the thermoregulation module 30 and circulation module
30 40, where included, to control temperature of the biological sample.

[00111] Preferably, an array of thermocouple sensors is implemented throughout device 10. In preferred embodiments, thermocouple sensors are integrated with the thermoregulation module 30 and circulation module 40. Thermocouple sensors may also be integrated with packaging system 60. An array of thermocouple sensors, or
5 any desired temperature sensor, would allow temperature to be recorded at a variety of positions within device 10 to gain a better understanding of the internal temperatures of the device 10 and the temperature of the biological sample, thereby optimising temperature. Positions that may be preferred for temperature sensors to be placed include the storage chamber 27, the packaging system 60, the heat
10 exchange system 30 and the circulation module 40, where used.

[00112] In embodiments, where temperature sensors – for example thermocouples – are included in the packaging system 60, electrical connection between thermocouple sensor or thermocouple sensor array may be provided by temporary connection. Such temporary connection may take the form of 'press stud' or any
15 other suitable system. This allows packaging system 60 to be disposed of along with the temperature sensor tip of the thermocouples without interfering with the architecture and operability of device 10.

[00113] In another embodiment, an infrared imaging or IR sensor system is used to implement the temperature monitoring system. This system would provide the
20 advantage that the temperature monitoring system need not be combined with the packaging system 60, which would allow it to be reused.

[00114] In one embodiment of the temperature monitoring system using an IR detector, an array may be used. This may take the form of numerous IR detectors which allow the temperature of the tissue to be analysed at various points in time
25 during transportation. In this embodiment, an IR array may be used to create an image or heat map to be displayed to the user, which would allow the system to detect areas of uneven temperature distribution on the tissue.

Electronic Control Unit 100

[00115] Electronic control unit (ECU) 100 is included within device 10 for automatic
30 temperature control of the heat exchange system 30 as well as automatic control over the circulation module 40 where this is included to allow circulation of warm/cold fluid from the circulation module to warm/cool the biological sample.

[00116] ECU 100 may actively control temperature, in one embodiment using feedback control, the operation of heat exchange system 30 being controlled as a function of temperature sensed by the temperature monitoring system 80. For example, if storage chamber 27 temperature is above setpoint, thermoregulation module 30 is operated to provide cooling. Where thermoregulation module 30 has heating functionality, and sensed temperature is below setpoint, thermoregulation module 30 is operated to provide heating.

[00117] ECU 100 may implement a range of temperature control programs, for example including the following:

- cooling of organ from body temperature to 4 to 8°C temperature range, or a desired temperature or temperature range specific to the biological being transported;
- preventing overcooling of the organ to below 4°C ;
- maintain desired temperature within the 4 to 8°C range, or a desired temperature range for the duration of transportation, while adjusting for variations to the external ambient temperature;
- increasing the temperature of the biological sample to a desired temperature, when warming function is required.

Each of these temperature control strategies may be adapted to different types of tissue, for example organs such as kidneys, hearts, lungs or livers. ECU 100 may include different temperature control logic for each type of tissue.

[00118] The above temperature control strategies may be implemented by ECU 100 control over any or all of the following, dependent on the variance of sensed temperature from desired temperature: heat exchange system 30, circulation module 40, heating or cooling element integrated with tissue protection module 50, heating element integrated with packaging system 60 (the latter being described below). Such temperature control using the ECU 100 is precise and may be accurate to $\pm 0.5^{\circ}\text{C}$.

[00119] ECU 100 may also enable wireless or wired communication of the device 10 with other computer systems in hospital systems or in transport vehicles. For example, a Bluetooth or other Wifi wireless communication system may be adopted.

- 25 -

[00120] ECU 100 may include inputs from sensors such as positioning sensors, orientation sensors and so on. HMI 124 may provide prompts for a user to perform a necessary operation.

5 [00121] Device 10 also preferably includes a display to show operating parameters, in particular biological sample temperature (or a suitable proxy temperature, e.g. storage chamber temperature), average biological sample temperature during transport and time since biological sample stored in the device and state of battery charge. Such display is conveniently coupled to ECU 100. An alarm may be provided to indicate any fault with the device 10 or the transport process.

10 [00122] The ECU 100 preferably includes a human machine interface (HMI) 124 for the user to interact with the device 10. Such HMI 124 may comprise buttons, a touch screen (which may be integrated with the display) or some other means to interact with the ECU 100. The ECU and HMI 124 is provided by battery 14 as shown in Figure 2.

15 [00123] In particular, a control strategy for ECU 100 and device 10 may be implemented by command entered through the HMI 124.

Packaging System 60

[00124] In preferred embodiments, the biological sample is packaged within a packaging system 60 to be disposed in storage chamber 27 of device 10. Packaging system 60 protects the biological sample whilst also providing a sterile environment. A two, three or plurality of bags may be adopted to ensure sterility in handling.

[00125] Adopting current practice, a three-layer bag system may be used as packaging system 60. An inner bag contains, for example, an organ which is sterile and surrounded by preservation solution. This bag is sealed in a sterile condition before being placed within another sterile bag before being sealed. This is followed by a third bag, which protects the inner bags from contact with an unsterile environment.

[00126] In an alternative embodiment, packaging system 60 may comprise two bags. In this embodiment, the tissue is contained within an inner sterile bag with preservation solution, and may be sealed by zip lock mechanism.

[00127] Optionally, the top of the packaging system 60 may be ripped by the user along a pre-weakened strip to facilitate sterile handling. The bags may be configured to stand flat on a flat surface like a table to facilitate easy handling. Optionally, the bags may also feature a double zip lock system to help prevent leaks.

5 [00128] In this embodiment, an outer bag is used to enclose and maintain the sterility of the inner bag(s). The inside of this outer bag is sterile, while the outside is not when in use. Optionally, the outer bag is configured to allow the outer edge of the bag to be rolled down to expose the inner bag, allowing easy handling and maintenance of sterile conditions of the inner bag(s).

10 [00129] In the above embodiments, it is to be understood that the packaging system 60 is disposable in order to maintain sterility and prevent cross-contamination between use.

[00130] The packaging system 60 may also comprise of other embodiments, including a rigid internal case, particularly for the storage of tissue samples such as cornea, skin and blood vessels. An outer bag, as described above, may be used to
15 accommodate the rigid case to maintain sterility.

[00131] In some embodiments, the packaging system 60 is combined with the circulation module 40. This would allow the circulation fluid to be circulated through the packaging system 60. This would allow the temperature of the packaging system
20 to be precisely controlled and may be implemented by having an inlet port and outlet port to the packaging system. This would allow a biocompatible solution to be circulated through the system.

[00132] In another embodiment, the packaging system 60 may be combined with the heat exchange system 30, to provide warming as described above. This may be
25 done by providing Peltier heating elements or resistive heating elements within the packaging system 60. The packaging system 60 may include electrical connectors that would enable it to be electrically connected to the body 11 of the device 10. This would allow electrical power from the device 10 to power the resistive heating elements in the packaging system 60 when the warming module is initiated, for
30 example.

[00133] In preferred embodiments, where suspending the biological sample is required, a local leaf seal may be used to ensure the tissue remains suspended in

the packaging system 60. This may be achieved by bonding small areas of both sides of a bag of the packaging system together, while leaving the majority unbonded. This would allow the biocompatible solution to flow freely within the bag and around the biological sample, preferably with minimal turbulent flow to maximise efficiency of heat transfer.

[00134] In preferred embodiments, a sealing clip is used to close the packaging system 60. This sealing clip 66 may use a long lateral closing arm that is sealed across the top of the bag. This would create a water-tight seal at the top of the bag while being readily openable.

10 *Energy Source*

[00135] Device 10 conveniently comprises an energy source to enable operation of the various components including ECU 100, heat exchange system 30, circulation module 40 and accessory components, for example being included in the packaging system 60 as described above. It will be understood that not all components are included in all embodiments as described above.

[00136] In one embodiment, the energy source is external to portable device 10, for example comprising a wired connection to an external energy source, such as mains electricity or an external computing device.

[00137] In another embodiment, though also useful as a backup to an external energy source, the energy source is provided by an on-board source such as a battery or photovoltaic cell. The battery 14 may be provided as a single unit or separated into a plurality of batteries. Preferably, the battery uses lithium-ion technology and is rechargeable. Battery 14 may be recharged by mains power or another source, for example a 12 V supply available on a transport vehicle carrying the device 10. Optionally, device 10 is powered by mains supply or 12V battery (e.g. located on a vehicle transporting device 10) whilst the battery 14 is recharging.

[00138] In some embodiments, the energy source may be provided using a combination of mains power, battery power or other power source.

[00139] The energy source may be selected to conserve on-board energy where provided. For example, in embodiments utilising a compressor-based refrigeration

- 28 -

system, mains power is desirably used when available with battery capability to allow for remote use.

5 [00140] The use of PCM based cooling in combination with circulation module 40 also reduces energy usage as a pre-primed PCM would not require a source of energy to achieve cooling. In embodiments using PCM based cooling, less power is used than for a compressor-based refrigeration system and extends the time the device 10 may be used away from mains electricity.

[00141] Preferred embodiments of the device 10 are now further described below.

10 [00142] Referring to Figure 3, device 10 comprises a heat exchange system 30 comprising separate cooling module 16 and heating module 17 allowing direct cooling and heating as required of tissue stored in storage chamber 27.

15 [00143] Cooling module 16, in this embodiment, comprises a chamber or container containing a PCM. The PCM changes state from solid to liquid or from liquid to gas, absorbing heat from the environment. In this way, cooling is achieved, which transferred into the biological sample via cooling of the storage chamber 27. For example, an ice/water mixture could be employed, if desired, with an additive such as a salt or compound to lower its freezing point. Cooling module 16 is conveniently configured to allow refilling whilst the device 10 is in use, for example by adding more ice.

20

[00144] Cooling module 16 may comprise a series of containers, for example as packages or blocks which contain the PCM. These blocks may be disposed about the storage chamber 27 surrounding the tissue and its packaging system 60 and enabling even cooling of the tissue. As the PCM is unpowered, this provides great flexibility as to the exact placement of the blocks since it is not necessary for the blocks to align with electrical plugs or sockets.

[00145] In further alternative embodiment, cooling module 16 may comprise both a PCM and Peltier cooler. Cooling module 16 may be arranged to allow for the majority of cooling to occur using a PCM, conserving power, with backup cooling being provided by the Peltier cooler. This embodiment allows the Peltier cooler to extend the lifetime of the PCM.

[00146] The separate heating module 17 of the embodiments described with reference to Figure 3 may provide heat by a variety of mechanisms, for example Peltier heating, resistive heating method or other method suitable for portable device 10. On command entered to HMI 124 and ECU 100, the heating module 17 begins a heating cycle. At this point, the heating module 17 may initiate a heating cycle to warm the biological sample. An automatic heating cycle is conveniently programmed into ECU 100 for this purpose.

[00147] The heating module 17 could be removable from the body 11 of device 10, separating it from the cooling module 16. Conveniently, heating module 17 – while containing the tissue – could operate through resistive heating with electrical connection to device 10. A wire extending between device 10 and heating module 17 would provide power to resistive heating element(s) allowing heating away from device 10, for example on a separate bench or table. Battery 14 or mains power could be used as energy source as with other embodiments.

[00148] Referring to Figures 4, 7 and 8, battery powered portable device 110 has similarities with the device of Figure 3. That is, separate cooling module 116 and heating module 117 are provided for the respective purposes of cooling and heating. Additionally, heat transfer is effected through inclusion of circulation module 40. Both cooling module 116 and heating module 117 are housed in respective insulated housings 116a and 117a to minimise undesired heat exchange between them and the outside environment.

[00149] Cooling module 116 may comprise a compartment or container for a PCM. This PCM – conveniently an ice/water mixture – may be refilled, as described with reference to Figure 3. The change of state of the PCM cools the circulating fluid and in combination with the circulation module, cools the biological sample. The packaging system 60 is suspended in the tissue protection module 50 with a heat conductive and flexible gel cushion 52. A thermocouple 82 located on the packaging system 60 provides temperature data to the ECU 100 and HMI 124. Thermocouple 82 could be substituted by an IR temperature sensor or other temperature sensor, an array of IR temperature sensors being shown in Figure 8.

[00150] In an alternative embodiment, cooling module 116 could include a block of frozen biocompatible solution or mixture (for example a eutectic mixture) which is used for heat exchange with the biological sample.

[00151] Circulation module 40 is placed in heat transfer contact with cooling module 116 by tubes 18 including valves 15. The tubes 18 are arranged in a serpentine configuration. This configuration allows circulation of fluid, driven by peristaltic pump 44, adjacent to the cooling module 116 as well as proximate to tissue in gel cushion 52. The pump 44, tubes 18 and valves 15 are located on a top panel 46 with inlet and outlet spigots 47 and 48 connectable to inlet tube 53 and outlet tube 54 of gel cushion 52. Further detail of this configuration is described herein.

[00152] Valves 15 are operated by ECU 100 to allow only respectively cooled or heated fluid to reach the storage chamber and preferably tissue protection module 50 – comprising cushions 52 – which is also preferably connected to the circulation module 40.

[00153] As shown, device 10 is in 'cooling' mode whereby cooled circulation fluid is driven, by the pump 44, from the cooling module 16 through tubes 18 before passing into the cushions 52 of the tissue protection module 50 as described in detail above. Cushions 52 are connected together to allow a flow of circulation fluid between cushions 52 allowing heat to evenly transfer from, i.e. cool, the tissue into the cushions 52. The flow of circulation fluid may be controlled by controlling pump 44 speed based on the temperature sensed by thermocouple 82.

[00154] In contrast, separate heating module 117 would allow warming of tissue surrounded by the tissue protection module 50. Heating module 117 may provide

heat to the circulation fluid by a variety of mechanisms, for example Peltier heating, resistive heating method or other method suitable for portable device 10. On command entered to HMI 124 and ECU 100, for example when a transplant operation is imminent, the heating module 117 begins a heating cycle. In this
5 embodiment, the heating cycle causes the valves 15 to change position (compared to the cooling cycle) and, with pump 44 operating, driving a flow of circulation fluid in heat transfer contact with the heating module 117. The heated circulation fluid evenly loses heat to the biological sample via the cushions 52 of the tissue protection module 50.

10 [00155] The circulating fluid used for heat transfer in cooling or heating the tissue via the circulation module 40 and tissue protection module 50 must be heat conductive but otherwise may take a variety of forms. Desirably, the circulating fluid would be a liquid with a freezing point below 0°C and a boiling temperature above 40°C. A range of liquids, such as ethylene glycol or polypropylene glycol, may be
15 suitable.

[00156] In an alternative embodiment, the cooling module 116 and heating module 117 are combined into a single unit. Such embodiment most conveniently includes a reverse cycle compressor-based refrigeration system or Peltier heater/cooler system. This embodiment would allow heat transfer via the circulation module 40
20 without need for use of valves 15 as the single unit heater/cooler allows active and precise control over temperature under control of the ECU 100.

[00157] Referring to Figure 5, device 10 has similarities with that of Figure 4, though also including circulation of fluid by circulation module 40 through the packaging system 60 as well as through cooling and heating modules 16, 17, tubing 18, valves
25 15 and pump 44. However, circulation through a tissue protection module 50 is omitted in favour of circulation through the packaging system 60. The packaging system 60 is still accommodated by the tissue protection module 50, cushions 52 supporting the packaging system 60 and the tissue within to reduce pressure injuries and facilitate even heat transfer.

30 [00158] The cooling module 16 may provide cooling by a PCM, Peltier cooler, absorption refrigeration or other suitable method for a portable device 10.

[00159] The heating module 17 may provide heating by a Peltier heater, resistive heating or other suitable method for a portable device 10. On command entered to HMI 124 and ECU 100, for example when a transplant operation is imminent, the heating module 17 begins a 'heating' cycle. In this embodiment, the heating cycle causes the valves 15 to change position (compared to the cooling cycle) and, with pump 44 operating, driving a flow of circulation fluid through the heating module 17. The heated circulation fluid flows into the packaging system 60 and evenly loses heat to, i.e. warms, the tissue within the packaging system 60.

[00160] In a further difference from the device 10 of Figure 5, the circulating fluid directly contacts the tissue. In this embodiment, the circulating fluid is a preservative or isotonic solution suitable for preserving the tissue within packaging system 60. For example, the preservative solution may be any suitable solution depending on the nature of the biological sample, for example Collins solution (e.g where tissue is a kidney), EuroCollins solution, phosphate buffered sucrose (PBS), University of Wisconsin solution and so on. Other solutions which could be employed may be selected, for example and as known to those skilled in the art, from the group consisting of Custodiol-N solution, histidine-tryptophan-ketoglutarate (HTK or Custodial Solution), Celsior solution, low potassium dextran glucose (LPDG or Perfadex) solution, EP4 (EP-TU) solution, ET-Kyoto solution and IGL-1 solution.

[00161] In other embodiments involving circulation fluids in direct contact with organs and tissues, other agents such as blood products, drugs and oxygen tissue, means or other agents beneficial for tissue or organ may be added to improve organ and tissue preservation, where indicated.

[00162] Temperature sensor(s) 82 may be positioned within the packaging system 60, the storage chamber 27 and/or tissue protection module 50 to allow accurate temperature readings to be obtained. ECU 100 receives temperature signals from temperature sensor(s) 82 as an input allowing control over heating or cooling in dependence on monitored temperature. ECU 100 may control heating or cooling in a range of ways including adjusting the flow rate of the pump 44, changing the position of the valves 15 and controlling the heating or cooling by adjusting power input to heating or cooling elements (where the output is electronically controllable). ECU 100 thus allows precise and even control over heating or cooling. Though automatic control mode may be preferred, manual control by a user via manual

inputs to HMI 124 is also an option. As examples, a user may prefer manual control over initiating a heating cycle or changing a temperature control programme based on tissue type.

5 [00163] As with the embodiment of Figure 3, the heating module 17 and cooling module 16 may be combined into a single unit operable as described above. This may be provided by a compressor-based refrigeration system or Peltier heater/cooler for example. This would allow flow of circulation fluid for heating or cooling without use of a valve system as the single unit allows active temperature control in cooling or heating mode.

10 [00164] Referring to Figures 6 to 12 and 15, there are shown embodiments of packaging system 60 for transporting a donor heart for transplant. Packaging system 60 includes a bag 61 which has a pocket formed by sealing of two walls of the pockets at different places 28 as shown in Figures 8 to 10. This ensures that the heart, or other organs and tissues, can be suspended in the bag 61 whilst the
15 circulation fluid passes around the organ or tissue freely through the bag 61. It also isolates the organ or tissue from potential injury through impact with the circulation module 40 or its tubing 18.

[00165] Packaging system 60 includes a sealing clip 66 running across the top of the bag 61, enabling a water tight seal to be formed following insertion of the heart.
20 Sealing clip 66 here consists of two hinged flaps 66a and 66b. One flap 66a has a cavity and the other flap 66b has a snap design that flexes to fit into cavity to generate positive locking of the bag 61.

[00166] Packaging system 60 may use a plurality of leaf seals 28, each leaf seal being disposed around the bottom half of the bag. Such arrangement prevents the
25 tissue within the packaging system 60 from slipping into the bottom of the bag 61 while still allowing a fluid, for example preservation fluid, to flow freely around the tissue, preferably in laminar flow.

[00167] Packaging system 60 includes temperature sensor 82 or an array of temperature sensors 82 which transmit temperature signals to ECU 100 and HMI
30 124 via connector 85 as shown in Figure 9. Temperature sensor 82 is conveniently a thermocouple. The use of connector 85 allows the packaging system 60 to be

disconnected from device 10 and disposed of following removal of the organ. The use of disposable packaging system 60 is desirable to ensure sterility on each use.

[00168] Packaging system 60 may, analogously with the gel cushion 52, be provided with an inlet tube 63 and an outlet tube 64 as shown in Figures 9 to 11.

5 The circulation fluid – whether or not a refrigerant – may be pumped into the packaging system 60, circulating through it, and then exiting via the outlet tube 64. Outlet tube 64 conveniently connects with the thermoregulation module 30 comprising cooling module 116 and heating module 117 for cooling or heating the circulation fluid. The circulation fluid is pumped back through packaging system 60
10 in the same manner as previously described for gel cushion 52. The distance of circulation of fluid travel between inlet tube 63 and outlet tube 54 may be selected and the packaging configured – for example with a tortuous fluid path or an inlet or outlet tube that extends almost to the bottom of the packaging system 60 to maximise heat transfer.

15 [00169] Packaging system 60 may comprise a bag which is capable of standing upright without support and which will not fall over when placed on a table or other flat surface.

[00170] Device 10 of Figure 6 may include a heating module 17 removable from the body 11 of device 10, separating it from the cooling module 16. Conveniently,
20 heating module 17 – while containing the tissue – could operate through resistive heating with electrical connection via heating connector 17a to device 10. Peltier heating could be used as an alternative.

[00171] A wire extending between device 10 and heating module 17 would provide power to resistive heating element(s) disposed around the heating module 17 to
25 enable even heating of tissue. The use of heating connector 17a allows separate removal of heating module 17 and tissue allowing heating away from device 10, for example on a bench or table. Battery 14 or mains power could be used as energy source as with other embodiments. In some embodiments, where a passive cooling module, such as a PCM is used, this would allow a heating cycle to bypass the
30 cooling action of the PCM and therefore achieve faster warming and consume less energy.

[00172] Referring to Figures 12 to 14, the tissue protection module 50 may be foldable allowing it to be flat packed for ease of manufacture and assembly. The tissue protection module 50 is made of a flexible heat conductive material that allows quick conduction of heat away from the organ and packaging system 60. Tissue protection module 50 contains a gel that remains in liquid phase at sub zero temperatures. Thus, the tissue protection module 50 acts as a gel cushion 52 reducing the chance of pressure injury to the organ due to the side walls of storage chamber 27. Tissue protection module 50 may be removed from the device 10 allowing rewarming of the organ prior to transplant where a heating element, as described above, is included.

[00173] Referring to Figure 15, the device 10 is provided with a heat exchange system 30 in the form of a temperature controlled refrigeration system 130 designed to maintain the biological at a desired temperature, i.e. 4-8°C, by use of a refrigeration cycle. In this system, a refrigerant fluid circulates within a closed loop to absorb and dissipate heat. The refrigeration system 130 has five main components: compressor 131, condenser 132, expansion valve 133, metallic tubing 135 and evaporator 137. Refrigerant flows between the various components through metallic tubing 135.

[00174] Compressor 131 compresses a refrigerant gas raising its pressure and temperature. In condenser 132, the hot high pressure refrigerant gas passes through the coils 132a of condenser 132 where it releases heat to the surroundings and the refrigerant condenses into a liquid.

[00175] In expansion valve 133, high pressure liquid refrigerant pressure drops causing the refrigerant to cool significantly and partially evaporate. In evaporator 137, cold refrigerant enters the evaporator coils where it absorbs heat from the biological and the storage chamber 27 causing the refrigerant to evaporate completely and return to compressor 131 as a low pressure gas.

[00176] Active control over the flow of refrigerant and compressor 131 operation by ECU 100 in response to temperature detected by temperature sensor 82 allows the biological to be held at a precisely controlled temperature. Further, a cooling programme can allow cooling of the biological sample at a controlled rate which prevents overcooling of the biological sample. Further, the use of a refrigeration

system allows rapid cooling in a matter of minutes and substantially less than an hour compared to using PCM alone.

5 [00177] Further, if refrigeration system, 130 is run in 'reverse cycle' it allows controlled warming. This feature may be advantageous in the context of organs and tissues for transplantation and blood products for transfusion. This is a feature absent in existing transportation technologies.

10 [00178] Referring now to Figure 16, showing a schematic diagram of the conventional practice in organ preservation. the diagram (a) shows a triple-bag system, where the organ is contained with the innermost bag suspended in preservation solution at 4°C, surrounded by a second bag containing crushed saline solution kept at -20°C, and contained within an outer bag that provides for sterility. The triple-bag system is contained within an insulated container filled with ice cubes. Below the diagram are graphs (b) and (c) showing the expected temperature conditions of the organ based on conventional practice based on mathematical modelling. The graphs show that the temperature of the organ falls to -3°C after 15 around 30 minutes and remains below 0°C for 8 hours, which is well below the desired temperature range for organ preservation at 4-8°C. This highlights that the conventional practice likely subjects organs and tissues to hypothermic injury.

20 [00179] Referring now to Figures 17(a)-(d), this Figure shows the results of a bench top experiment whereby a piece of chicken breast was cooled from body temperature ($T_0=36^{\circ}\text{C}$) to 4-8°C using passive cooling with a commercial PCM with a melting point of -5°C as indicated in Figure 17(a). In brief, a sample of chicken breast of similar mass to a human heart (480 g) was selected to simulate an organ. Starting conditions are shown in Figure 17(b). Specifically, the chicken breast was 25 at a starting temperature of 36°C at T_0 and placed in a litre of saline solution at 4°C. To this mixture, a PCM was added (2520 g) at a temperature of -5.3°C. A temperature sensor was placed inside the centre of the chicken breast. This whole assembly was placed in an insulated box and the lid closed. This experiment showed that the chicken breast slowly reached 5.5°C after 2-3 hours, and was maintained 30 at the target temperature of 4-8°C for 6.5 hours as shown in Figures 17(c) and (d). This shows that while a PCM-only system can deliver the safe temperature conditions, time to target temperature (8°C) was very long (1 hour 30 minutes), especially given that the limit for warm ischaemia of a donor heart is 3-4 hours. In

addition, the PCM was only able to maintain the target temperature for a limited time before being exhausted and needing to be replaced.

5 [00180] Referring now to Figures 18(a)-(f), this shows the results of a bench top experiment (with cooler set up as shown in Figures 18(a) and (b), (b) showing the temperature sensors) whereby a piece of chicken breast was cooled from body
10 temperature to 4-8°C using passive cooling with a commercial PCM with a melting point of -25°C. As in the experiment shown in Figure 17, starting conditions are shown in Figure 18(c). Specifically, a sample of chicken breast (480 g) at a starting temperature of 36.5°C at T_0 was placed in a litre of saline solution at a starting
15 temperature of 4°C. To this mixture, a PCM was added (2406 g) at a temperature of -5.3°C. A temperature sensor was placed inside the centre of the chicken breast. This whole assembly was placed in an insulated box (as shown in Figures 18(a) and (b)) and the lid closed.

15 [00181] The results in Figures 18(d) and (f) show that the chicken breast reached a temperature below 8°C after 47 minutes and remained below 8°C for a total 13 hours. While the cooling was faster compared with the previous experiment using -5°C PCM, the chicken breast fell below the safe lower temperature limit of 4°C for a significant duration. This shows that a colder PCM in isolation, without circulation of
20 a circulation fluid by circulation module 40 though allowing quicker cooling than PCM cooling alone (as described for the experiment outlined by Figure 17), risks overcooling the organ, similar to conventional practice, and could lead to hypothermic injury to organs.

25 [00182] Referring now to Figures 19(a)-(f), this shows the experimental data obtained from a simulation of a portable device as described with reference to Figure 4 of this specification and schematically shown in Figures 19(a) and (e). In brief, a reservoir (centre block) of PCM (1980 g) and water (1800 mL) was created with starting conditions tabulated in Figure 19(b). This fluid was pumped into a bag containing the chicken breast (420 g) at 36°C and water at 4°C (1480 mL). A temperature sensor was placed inside the centre of the chicken breast. This whole
30 assembly was placed in an insulated box and the lid closed. The temperature was monitored for 24 hours.

[00183] The graphs of Figures 19(c) and (d) show that a temperature of 8°C was reached in 35 minutes. The chicken breast temperature never fell below 4°C and

maintained within a safe temperature of 4-8°C for 5 hours with the key results shown in Figure 19(f). This shows that a PCM system combined with a circulation module and an electronic control unit as described in this specification can deliver significantly faster cooling and safer temperature profile.

5 [00184] Throughout this specification, unless the context requires otherwise, the word "comprise" or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

10 [00185] The invention described herein may include one or more range of values (eg. volume, temperature etc). A range of values will be understood to include all values within the range, including the values defining the range, and values adjacent to the range which lead to the same or substantially the same outcome as the values immediately adjacent to that value which defines the boundary to the range. Accordingly, unless indicated to the contrary, the numerical parameters set forth in
15 the specification and claims are approximations that may vary depending upon the desired properties sought to be obtained by the present invention. Hence "about 80%" means "about 80%" and also "80%". At the very least, each numerical parameter should be construed in light of the number of significant digits and ordinary rounding approaches.

20 [00186] Other definitions for selected terms used herein may be found within the detailed description of the invention and apply throughout. Unless otherwise defined, all other scientific and technical terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which the invention belongs.

25 [00187] Each document, reference, patent application or patent cited in this text is expressly incorporated herein in their entirety by reference, which means that it should be read and considered by the reader as part of this text. That the document, reference, patent application or patent cited in this text is not repeated in this text is merely for reasons of conciseness.

30 [00188] Any manufacturer's instructions, descriptions, product specifications, and product sheets for any products mentioned herein or in any document incorporated

by reference herein, are hereby incorporated herein by reference, and may be employed in the practice of the invention.

5 [00189] The present invention is not to be limited in scope by any of the specific embodiments described herein. These embodiments are intended for the purpose of exemplification only. Functionally equivalent products, formulations and methods are clearly within the scope of the invention as described herein.

CLAIMS

1. A portable device for transporting a biological sample comprising:
 - (a) a housing accommodating a storage chamber for receiving the biological sample;
 - 5 (b) a thermoregulation system for adjusting temperature of the storage chamber comprising:
 - a heat exchange system for exchanging heat between the biological sample and the storage chamber;
 - a temperature monitoring system for sensing temperature of the biological sample and the storage chamber; and
 - 10 a controller for actively controlling operation of the heat exchange system and storage chamber temperature dependent on temperature sensed by the temperature monitoring system,
- 15 wherein said controller operates said heat exchange system to control storage chamber temperature according to a selected temperature control program as commanded by the controller.
2. The portable device of claim 1, wherein said heat exchange system includes a heating module for rewarming the biological sample according to a rewarming temperature control program.
- 20 3. The portable device of claim 1 or 2, wherein said selected temperature control program controls temperature of the storage chamber within a selected temperature range, said selected temperature range having a lower temperature limit and an upper temperature limit; and
- 25 wherein said thermoregulation system provides heating if sensed temperature is below the lower temperature limit; and
wherein said thermoregulation system provides cooling if sensed temperature is above the upper temperature limit.
4. The portable device of any one of the preceding claims, wherein said rate of temperature change of said storage chamber and biological sample is precisely controlled.
- 30

5. The portable device of any one of the preceding claims, wherein said temperature control program is selected dependent on the nature of the biological sample.
6. The portable device of any one of the preceding claims, wherein the controller is programmed with a plurality of temperature control programs selectable dependent on the nature of the biological sample.
7. The portable device of any one of the preceding claims, further comprising a circulation module for pumping a circulation fluid to facilitate heat transfer between the heat exchange system and a biological sample when received in the storage chamber.
8. The portable device of any one of the preceding claims, comprising a tissue protection module for providing mechanical protection of the biological sample, preferably aiding in temperature control.
9. The portable device of claim 8, as dependent from claim 7, wherein the circulation module pumps the circulation fluid through the tissue protection module.
10. The portable device of claim 9, wherein said tissue protection module comprises at least one cushion for said biological sample, wherein the cushion is filled with at least one of a gel, a gas, a liquid or a semi-solid, each material being heat conductive.
11. The portable device of any one of claims 8 to 10, wherein said tissue protection module comprises at least one heating element, optionally being a resistive heating element or a Peltier heating element.
12. The portable device of claim 10, wherein said at least one cushion is filled with a low viscosity gel.
13. The portable device of any one of claims 7 or 9 to 12, comprising a packaging system for the biological sample, wherein the circulation module pumps the circulation fluid through the packaging system, preferably in a manner that minimises turbulent flow.
14. The portable device of claim 13, wherein the packaging system comprises at least one element optionally being a resistive heating element or a Peltier element and an electrical connector allowing connection to an energy source of the device.

15. The portable device of claim 13 or 14, wherein the circulation fluid directly contacts the biological sample.
16. The portable device of any one of the preceding claims, wherein the thermoregulation system comprises a phase change material for providing cooling.
- 5 17. The portable device of any one of the preceding claims, wherein the heat exchange system comprises a cooling system selected from the group consisting of a compression refrigeration system, an absorption refrigeration system and a Peltier cooling system.
- 10 18. The portable device of claim 17, wherein said cooling system is also operable in a heating mode.
19. The portable device of any one of the preceding claims, wherein the controller is configured to detect a fault and operate the device according to a fault mitigation strategy.
- 15 20. The portable device of any one of the preceding claims, comprising a user operable device to achieve a selected temperature range, optionally by user induced activation of a phase change material.
21. The portable device of any one of the preceding claims, comprising a packaging system for the biological sample, said packaging system comprising:
 - 20 a primary container housing the biological sample; and
 - a secondary container accommodating the primary containerwherein the secondary container protects the biological sample from mechanical injury.
22. The portable device of claim 21, wherein at least one of said primary container and said secondary container is a bag comprising said tissue protection module
- 25 providing a cushion for said biological sample.
23. The portable device of claim 22, wherein said bag is configured to allow fluid flow, preferably laminar fluid flow or reduced turbulent flow, around said biological sample.
24. A method of controlling temperature of a biological sample comprising:
 - 30 (a) receiving the biological sample in a storage chamber of a portable device;

- 43 -

- (b) adjusting temperature of the storage chamber with a thermoregulation system comprising a heat exchange system for exchanging heat between the biological sample and the storage chamber;
- 5 (c) sensing temperature of the storage chamber; and
- (d) actively controlling operation of the heat exchange system and storage chamber temperature dependent on the sensed temperature,
- 10 wherein said heat exchange system is controlled according to a selected temperature control program.
25. The method of claim 24, comprising cooling the biological sample according to a cooling temperature control program or rewarming the biological sample according to a rewarming temperature control program.
26. The method of claim 24 or 25, wherein said temperature control program is
- 15 selected dependent on the nature of the biological sample.