Title

Vascularized laboratory device, method for characterizing, studying, quantifying, diagnosing, prognosticating, testing, simulating, modeling, transplanting or growing a normal or disease state of an animal or of a human being, and method for treating an animal or a human being

Field of the application

The application deals with methods for characterizing, studying, quantifying, diagnosing, prognosticating, testing, simulating, modeling, transplanting or growing a normal or disease state of an animal or of a human being, and with a method for treating an animal or a human being.

Summary

A Method comprises the following steps:

- extracting a predetermined part of the body,
- implanting the extracted part of the body at/in another location in the body,
- subjecting the implanted part of the body to a predetermined treatment,
- observing the treated part of the body.

A method for treating an animal or a human being comprises the following steps:

- performing the steps of testing the effectiveness of two or more treatments on two or more parts of a body of an animal or of a human being at the same time with

the steps according to one or more of the aforementioned claims,
- selecting the most effective treatment, and
- treating the body of the animal or human being according to the selected treatment.

A device for receiving a part of a body of an animal or of a human being comprises the following features:
- a block device of biocompatible material,
- a detachable covering means of biocompatible material,
- at least one receiving area provided by the block device and the covering means,

wherein at least the block device comprises duct means extending between at least one outer surface area of the block device and the at least one receiving area.

A method comprises the following steps:
- implanting a receptacle device at a predetermined location of the body, the receptacle device being formed to receive at least one predetermined part of the body,
- waiting a predetermined time for the predetermined part of the body being received in the receptacle device,
- evaluating the predetermined part of the body being received in the receptacle device.

A Method for treating an animal or a human being, the method comprising the following steps:
- performing the steps of testing the effectiveness of two or more treatments on two or more parts of a body of an animal or of a human being at the same time with the steps according to one or more of the aforementioned claims,

- selecting the most effective treatment, and
- treating the body of the animal or human being according to the selected treatment.

Device for receiving a part of a body of an animal or of a human being, the device comprising the following features:
- a block device of biocompatible material,
- at least one receiving area provided by the block device,

wherein the block device comprises duct means extending between at least one outer surface area of the block device and the at least one receiving area.
Covering means for use with a block device, the covering means being mechanically compatible with the block device.

A block device for use with a covering means is mechanically compatible with the covering means.

Subject Matter of the application

The application deals by way of example with vascularized laboratory devices, with methods for characterizing, studying, quantifying, diagnosing, prognosticating, testing, simulating, modeling, transplanting or growing a normal or disease state of an animal or of a human being, and method for treating an animal or a human being.

An example method according to the application comprises the following steps:
- moving a predetermined part of the body to another location in the body,

- keeping the moved part of the body alive by supplying and/or integrating it with blood vessels or inducing the formation of blood vessels,
- subjecting the moved part to a predetermined treatment,
- observing the treated part of the body

A further method according to the application comprises the following steps:

- performing the steps of testing the effectiveness of two or more treatments on two or more parts of a body of an animal or of a human being at the same time with the steps according to one or more of the aforementioned claims,
- selecting the most effective treatment, and
- treating the body of the animal or human being according to the selected treatment.

An example device according to the application for receiving a moved part of a body of an animal or of a human being comprises the following features:

- a block device of biological and/or biocompatible material,
- a detachable covering means of biological and/or biocompatible material,
- at least one receiving area provided by the block device and the covering means,

wherein at least the block device comprises duct means extending between at least one outer surface area of the block device and the at least one receiving area.

A further example method according to the application comprises the following steps:

- implanting a receptacle device at the location of the body, the receptacle device being formed to receive at least one predetermined part of the body,
- waiting a predetermined time for the predetermined part of the body being received in the receptacle device,
- evaluating the predetermined part of the body being received in the receptacle device.

Covering means according to an example of the application for use with a block device are mechanically compatible with the block device as well as a block device according to the application for use with a covering means are mechanically compatible with the block device.

An example method to keep viable a predetermined part of an animal or of a human being after the part is moved to another location in the body by supplying and/or integrating the part with blood vessels in the new location or inducing the part per se to produce its own blood vessels.

The step of “moving” can be achieved by different means like surgical excision or biopsy followed by transplantation of the part into a new location. Or it can be achieved by inducing chemotactic attraction causing auto-migration of the part into a new location. Or it can be achieved by electrophoresis of the part into a new location. Or it can be achieved by any form of electromagnetic or magnetic manipulation of the part into a new location. Or it can be achieved by antibody trapping of the part into a new location. Or it can be achieved by chemical trapping of a part into a new location. Or it can be achieved by simple passive diffusion of the part into a new location down a gradient.

The expressions "portion" and "part" will be used as synonyms throughout the description. The moved part, instead of moving it into another location in the body of the same person or animal or portion - can also be implanted into another body.

A further method to simulate, model or grow the moved part in the new location to resemble another normal or disease state of an animal or of a human being or to develop a transplantable part.

A further method to study, characterize, diagnose, prognosticate or quantify any responses of the moved part in the new location by subjecting it to changes in its environment or subjecting the moved part to a predetermined treatment.

The aforementioned “responses of the moved part” include any physical, chemical, biochemical, physiological, genetic (that is relating to genes), molecular, chromosome, nuclear, nucleoplasm, transcription, translation, organelle, cytoplasm, cyto-skeleton, cell-cycle, signal transduction pathways, membrane, membrane conductance, membrane receptor, cellular, cell division, cellular movement, endocytosis, exocytosis, secretion, cell-to-cell interaction or extracellular matrix, etc, changes.

A further method for predicting the effectiveness of a predetermined treatment on the original part from which the moved part came from by subjecting the moved part to testing by the same treatment first. The method comprises the step of

- moving a predetermined part or portion of the body to a new location,
- subjecting the moved part of the body to a predetermined treatment,
- observing the treated part of the body for any changes,
- subjecting the original part of the body from which the moved part came from to the same predetermined treatment.

The “treated part of body” being the predetermined part or portion of the body which was moved from the original part.

The “predetermined treatment” can be achieved by delivery of different molecules like chemicals, drugs, herbs, hormones, growth factors, chemokines, interleukins, extracellular matrix, genes, double-stranded RNAs (eg. small interfering RNAs, micro-RNAS, hair-pin RNAS), plasmids (eg. recombinant), antibodies, antigens, peptides, proteins, carbohydrates, lipids, ions, free radicals, oxygen, radiolabelled molecules, fluorescent-labelled molecules, microorganisms, cells etc or radiation. Delivery of molecules can be achieved by different means like, passive diffusion, active pumps, transfection, infection, lipofection, electroporation, electrophoresis, etc. Radiation can be delivered externally from a specialized machine or internally via radiation seeds.

A further step comprises determining the outcome of the treatment, which means whether the treatment is successful or not. A therapy on the original part would require a successful treatment of the moved part that came from it.

According to the step of “observing the treated part of the body” includes an optional step of purging or extracting liquid or gas (eg. carbon dioxide, oxygen) or solids or ions (eg. hydrogen ions) or molecules or proteins or carbohydrates or lipids or nucleic acids or chromosomes or organelles or antigens or antibodies or cells or tissue or apoptotic bodies or blood or serum or interstitial fluid or extracellular matrix etc, from the treated part of the body and a step of measuring predetermined characteristics of the same. The expressions "purging" and "extracting" are synonyms here.

The step of “observing the treated part of the body” may include an optical verification (eg. direct microscopic imaging or confocal microscopic imaging or fluorescence imaging or bioluminescence imaging etc) or verification with other electro-magnetic radiation like X-Ray, CT Scan, MRI, Positron Emission Tomography (PET) imaging, thermo imaging, infrared imaging etc or mass spectrophotometer verification.

Before the step of moving the predetermined part of the body to another location in the body, there may be provided a step of implanting a receptacle device at the location of the body, the receptacle device being formed to receive the moved part of the body.

The receptacle device is left such a time within the body that at least one contact area for receiving the moved part of the body is vascularized, which means that it has blood vessels for supplying the device with blood of the body at the time when the part of the body is being moved into the receptacle device. Or the part of the body may be moved into

the receptacle device first and left for such a time until vascularization occurs in the moved part.

According to the application, at least one part of the receptacle device may be replaced by a covering means at the time of the predetermined part of the body being moved into the receptacle device or at a time when the cover needs to be changed for different reasons like, re-fill of predetermined treatment, change of predetermined treatment, cover not working properly, etc.

The step of implanting the receptacle device at the location of the body can be done either such that the receptacle is covered fully under a skin portion of the body or such that the receptacle is partially underneath a skin portion of the body, partially protruding from the body similar to a tooth or in deeper tissues of the body or in a body cavity or in the bones of a body.

One end of this vascularized device can be the arterial end while the other end can be venous or both ends may belong to at least one capillary. The spaces in the device may be filled with normal pieces of bones or bones that are affected by diseases like leukemia, lymphoma, multiple myeloma, myelodyplastic syndrome, metastatic solid cancers to the bone etc. The cover can be surgically removed and the empty spaces in the device can be exposed. A new biological or biocompatible cover may then be fitted over the device converting the open spaces into enclosed vascularized chambers.

A method for treating an animal or a human being comprises the following steps:

- performing the steps of testing the effectiveness of two or more treatments on two or more parts of a body of an animal or of a human being at the same time with the steps according to the above mentioned steps,
- selecting the most effective treatment, and
- treating the body of the animal or human being according to the selected treatment.

The treatment can involve the whole body or part of it. The selected treatment may be the apparently most effective treatment.

The method for treating an animal or a human being according can include that during the step of treating the body of the animal or human being according to the selected treatment the aforementioned steps are continued. This is done because the body may change its reaction to the treatment with the selected method. Further studies of possible interactions between treatments can also be achieved.

The application includes a device for receiving a part of a body of an animal or of a human being with the following features:

- a block device of biological or biocompatible material which may be prefabricated,
- a detachable covering means of biological or biocompatible material,
- at least one receiving area provided by the block device and the covering means, the receiving area comprising the shape of a space, a cavity, or a porous area,

wherein at least the block device comprises duct means extending between at least one outer surface area of the block device and the at least one receiving area. The duct means are provided for various purposes, e.g for vascularizing the receiving area or for providing channels for communication with the outside of the body for providing substances into the receiving area or for extracting substances from inside the receiving area.

The device and parts of it may comprise “biological material” and “biocompatible material”. Throughout the application, “biological material” may comprise bone mineral material and substances such as bone morphogenetic protein-7 (BMP7) or cells such as stem cells which may be added to stimulate development of the bone mineral block into solid bone when implanted in the body. Throughout the application, “biocompatible material” may comprise biocompatible polymers eg. polydimethylsiloxane (PDMS) as well as titanium or other biocompatible substances. “Biocompatible material” are materials that when implanted into the body of a human or of an animal, will not elicit a host immune response that results in the rejection of the implant or internal injuries to the host at the implant site through unwanted inflammatory processes.

The device may comprise angiogenesis growth factors which are mixed in a biocompatible solvent, in a solution, in a gel or which are provided in solid form. The device may further comprise stem cells, endothelium activating factors like interleukin-1β or TNFα, selectins, integrins, chemokines, antibodies, extracellular matrix.

According to the application, two or more of the at least one receiving areas are provided. At least one receiving area may comprise a detachable filling means, e.g. in the form of reciprocal plugs or stoppers. The filling means may be a part of the covering means.

The covering means according to the application may be provided to be mechanically compatible with the block device and the covering means may comprise biocompatible material and other materials mentioned above for the whole device.

The covering means may provide not only one but two or more receiving areas.

The covering means may further provide at least one internal reservoir in the vicinity of at least one receiving area, wherein at least one internal reservoir may comprise at least one interconnecting duct extending between the reservoir and the receiving area.

The duct may comprise an operable valve for at least partly opening or at least partly closing the duct, the valve is operable by external or remote means. The valve may also be a dissolvable wall or membrane.

The duct may also comprise an operable pump for transporting a substance contained from the reservoir to the receiving area. The pump and valve may operable by external or remote means. The valves and ducts may be designed to channel these agents into their respective vascularized chambers for in vivo experimental analysis.

The internal reservoir may be pre-filled with therapeutic or analytical agents. These may include, chemicals, drugs, herbs, hormones, growth factors, chemokines, interleukins, extracellular matrix, genes, double-stranded RNAs (eg. small interfering RNAs, micro-RNAS, hair-pin RNAS), plasmids (eg. recombinant), antibodies, antigens, peptides, proteins, carbohydrates, lipids, ions, free radicals, oxygen, radio-labelled molecules, fluorescent-labelled molecules, microorganisms, cells etc.

The invention comprises also a block device for use with a covering means, the covering means being mechanically compatible with the block device. The block device may comprise biocompatible material and other materials mentioned above for the whole device.

The block device according to the application may comprise not only one but two or more receiving areas. At least one internal reservoir may be provided in the vicinity of the receiving areas. At least one internal reservoir may comprise at least one interconnecting duct extending between the reservoir and the receiving area. The arrangement of the reservoirs in the block device may be similar to those in the covering means, including ducts, valves and pumps. The respective features of the covering means apply to the block device.

The block device according to the application may be made of bone. A prefabricated block may comprise bone mineral material, osteogenic factors (eg. bone morphogenetic protein-7 etc), stem cells and titanium plates or meshwork to be implanted into the body whereupon which the bone mineral block

is stimulated to develop into solid bone comprising cortical bone and bone marrow elements.

The block device and cover means according to the application may be made of biocompatible polymer eg. polydimethylsiloxane (PDMS) or titanium or other biocompatible substances.

The block device and cover means according to the application may be made in the macro-scale or micro-scale or a combination of both. “Macroscale” in this application refers to devices whose dimensions are above 1000 micrometers. “Microscale” in this application refers to devices whose dimensions are below 1000 micrometers.

The block device and cover means according to the application may be made in the form of a PDMS microchip device. PDMS device fabrication of block and cover may broadly include steps of designing and fabricating a silicon wafer master, pouring PDMS prepolymer on the silicon master and curation, peeling PDMS replica from the silicon master, exposure PDMS replica to oxygen plasma and attaching to mating surface.

The application also comprises a method for characterizing a state of a body of an animal or of a human being. The state of the body can be normal or diseased. Characterizing here is determining the characteristics of a disease and it is a pre-step to diagnosing the disease. Later diagnosing and identifying of the disease is also a part of the application.

The method comprises the steps of

- implanting a receptacle device at the location of the body, the receptacle device being formed to receive at least one predetermined part of the body, which may include cells and tissues, or blood with circulation substances such as cancer cells, micro-organisms - as bacteria, fungus, parasites - bio-markers, etc.
- waiting a predetermined time for the predetermined part of the body being received in the receptacle device,
- evaluating the predetermined part of the body being received in the receptacle device.

The step of "waiting" does not mean that nothing is done but it expresses that there may be some time between implanting the device and the step of evaluating the content of the device. In the case of evaluating simple liquids like blood or body liquid the delay between implanting and evaluation may be rather short. In the case of catching certain cells, the delay may be longer.

The receptacle device is left such a time within the body that at least one contact area for receiving the moved part of the body is vascularized, which means that it has built up blood vessels for supplying the device with blood of the body, at the time of implanting the moved (portion) part of the body into the receptacle device or after the predetermined part of the body has moved in.

At least one part of the receptacle device may be replaced by a covering means before the step of waiting a predetermined time for the predetermined part of the body being received in the receptacle device.

At least one part of the receptacle device is replaced by a covering means after the step of waiting a predetermined time for the predetermined part of the body being received in the receptacle device and before the step of evaluating the predetermined part of the body being received in the receptacle device.

Other features of the device used for the latter method may be chosen similar to the device used for the methods which were described initially. This applies to all aspects of the respective devices, such as materials, appliances, parts, components, etc.

Special forms of reservoirs and valves shown in US 20070016163 and US 20070036835, which are incorporated here by reference. Proprietary reservoir arrays, drugs or biosensors can be stored within the reservoirs, thereby protecting these reservoir contents from the environment (e.g., a patient’s body) until they are needed. Preprogrammed microprocessors, wireless telemetry, or sensor feedback loops can provide active control of the opening of the reservoirs to initiate drug release or expose enclosed biosensors, thus giving the physician or patient greater control over therapy. Alternatively, layers or other combinations of controlled release, polymeric matrices can provide passive control of the release or exposure of the reservoir contents in applications that do not require microprocessors or power sources.

When one provides a receiving area which is connected with blood vessels, pressure is likely to build up in the reservoir, the pressure being caused by interstitial fluid col-

lection build-up. This is due to fluid which leaves the blood vessel and enters the receiving area. A connecting drainage reservoir may be provided for that, the drainage reservoir being connected with the receiving area by a special duct. Further, a drainage duct leading from the drainage reservoir to the outside of the device may be provided.

Further Advantages of the subject matter

This generic method and design to create in vivo vascularized laboratory devices is the result of the author's search for innovative solutions to treat cancer patients resistant to standard treatments. Although the subject matter can also be used in other non-cancer domains, its nature and functions are well understood from its origin in solving problems associated with treatment-resistant cancer.

Many cancer patients suffer from a relapse of their cancer and resistance of their cancer to standard treatments. These cases pose significant challenges to the oncologist who has to resort to trial and error strategies which often fail. The application contributes to the current state-of-the-art strategy of cancer treatment. Right from the moment of pathological diagnosis from biopsy samples, the application provides for a better characterization within the existing classification system for naming diseases. Our nosology is based on a historical nomenclature of anatomical and histological terms. It thus enables the experimenter to uncover different underlying molecular mechanisms that may result in the same histological or anatomical appearance. More importantly, it allows a real-time observation and matching of our fixed nomenclature of diseases does with the reality of

ongoing changes in diseases over time. Hence disease 'X' over time may evolve into 'Xa' or 'Xb' in different individuals and these important transformations can now be reflected in the standard name 'X'. This makes it possible to avoid blind lumping of apparently similar but actually different diseases in clinical trials. Hence the strategy of clinical trials solves the problem of treatment-resistant cancer cases at the individual level.

The application provides a technology that will allow us to detect very early response of cancer to treatment. Current imaging techniques like Magnetic Resonance Imaging (MRI), CT Scans and standard X-rays use changes in tumor size as the criteria for anatomical response to therapy. But major changes in tumor volume tend to occur late after the start of treatment and this can be observed. Hence, treatment is considered effective when there is a large decrease in tumor size indicated by consecutive images measured 3 to 4 months later. The application provides a reduction in time of diagnosis in the face of fast-growing cancers that are repeatedly resistant to standard treatments based on clinical trial data. More cutting-edge technologies like FDG-PET scan and Diffusion-weighted MRI may be able to cut down the waiting period to a week or more depending on tumor type, but no technology exists to date to reliably detect whether the tumor is responding to therapy or not within a day or two. This time factor for early detection of tumor responsiveness is clearly important since the earlier we know that a tumor is not responding to certain drugs, the earlier we can switch treatment strategies to find the right therapeutic drug/s for the patient. Instead of waiting weeks later when the patient's functional status has already deteriorated

from disease progression and he or she may no longer be able to tolerate further treatment.

Moreover FDG-PET scan and Diffusion-weighted MRI indirectly predict tumor responsiveness by measuring changes in metabolic activity and intracellular water movement respectively. The application provides a method or technology to provide us a direct assessment of tumor apoptosis or programmed cell death in the human body, which is the gold standard of treatment efficacy. This is true also for blood malignancies like leukemia which is more 'fluid' in nature and does not exist as a solid tumor.

The application provides a method which, once the cancer in the body is being treated via intravascular administration of therapeutic agents, there is more than only one chance of getting it right. If the cancerous tissues in one receiving area do not respond, then one is left knowing whether the biological profile of the tumor has changed significantly from the failed treatment or not by simply referring to another receiving area.

One is also not left without knowledge of whether the failure is due to inadequate concentrations of therapeutic agent/s reaching the cancer cells in the tumor, i.e. pharmacokinetics, OR whether the failure is due to problems associated with drug-target interactions i.e. pharmacodynamics. Several receiving areas which are run under different conditions provide different information at the same time.

Hence in the standard of care according to the application, once treatment is administered and the cancer does not re-

spond, we are not left with unknowns. The default assumption then almost always lean towards pharmacodynamic inefficacy and the tumor is then rightly or wrongly considered to be resistant to that particular therapeutic agent/s without convincing proof.

Also, the application enables the use of cancer cell cultures or animal cancer models to predict cancer response to treatment suffers from difficulty in exactly matching the actual tumor and its environment in the human body. These techniques may be useful clinically to treat patients at the bedside.

This method and subject matter of creating novel vascularized laboratory devices in vivo seeks to resolve all the aforementioned inadequacies present in the state-of-the-art treatment of cancer. Other novel in vivo vascularized laboratory devices for analytical purposes besides cancer can also be created using the same method to generate vascularization of the device in vivo. Tissue engineering work has been done in humans and pigs on growing a vascularized bone graft in vivo and transplanting it thereafter to repair bone defects. However, this is not a method for creating vascularized laboratory devices in vivo as described by this invention.

This application documents a generic method and design for creating vascularized laboratory devices in vivo. These devices may be constructed in different scales of science, that is macro- and micro-sciences, using the same method and design. Materials used to fabricate the scaffold of a device can be biological materials eg. bone or biocompatible mate-

rials eg. polydimethylsiloxane (PDMS) or titanium. The device is initially filled with angiogenesis growth factors which may be mixed in a biocompatible solvent or solid, with or without stem cells. It is then implanted in the body to generate new blood vessels in it. The in vivo vascularized device may be used for different analytical purposes. Per se, it may be used as a base for analysis of blood vessels and blood contents. A unique detachable cover and reciprocal plug-cavity design creates spaces in the device to receive and house transplanted living tissues, eg. cancerous tissue, or cells. These living tissues or cells are kept viable in the vascularized chambers of the implanted device hence making them amenable to experimental analysis in vivo.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1A shows a prefabricated bone device according to the application,

Figure 1B shows vascularization of the device of Figure 1A,

Figure 1C shows attachment of a second cover to the in vivo vascularized bone device of Figure 1B,

Figure 2A shows a polydimethylsiloxane (PDMS) MEMS (Micro-Electro-Mechanical Systems) device of the application,

Figure 2B shows vascularization of the micro-device in vivo of Figure 2A,

Figure 2C shows attachment of a second cover to the in vivo vascularized MEMS (Micro-Electro-Mechanical Systems) device of Figure 2B.

Figure 3A shows a polydimethylsiloxane (PDMS) MEMS Micro-Electro-Mechanical Systems) device of the application,

Figure 3B shows vascularization of the micro-device in vivo of Figure 3A

Figure 3C shows extravasation of circulating tumors cells into the chamber

DETAILED DESCRIPTION OF THE INVENTION

Figure 1A shows a prefabricated bone device made of bone mineral block and a unique reciprocal plug-cavity cover design. The device is impregnated with angiogenesis growth factors with or without stem cells and is subsequently implanted in vivo. Bone morphogenetic protein-7 (BMP7) may be added to stimulate development of the bone mineral block into solid bone.

Figure 1B shows vascularization of the device in vivo as a result of angiogenesis being stimulated by the growth factors. The bone mineral block also develops into solid bone. The cover is surgically removed and diseased bone fragments may be transplanted into the empty cavity or chamber of the device.

Figure 1C shows attachment of a second cover to the in vivo vascularized bone device. This new cover is fabricated to contain internal reservoirs with interconnecting valves and ducts. The internal reservoirs are pre-filled with therapeutic or analytical agents while the valves and ducts are designed to channel these agents into the chamber for in vivo experimental analysis on the transplanted diseased bone.

Figure 2A shows a polydimethylsiloxane (PDMS) MEMS (Micro-Electro-Mechanical Systems) device or cartridge with a unique reciprocal plug-cavity cover design. When the cover is closed, interconnected spaces in the chambers and ducts that open to the outside are filled with angiogenesis growth factors with or without stem cells. The device is then implanted in vivo.

Figure 2B shows vascularization of the micro-device in vivo as a result of angiogenesis being stimulated by the growth factors. The cover is surgically removed and tissue eg. cancerous tissue or a collection of cells may be transplanted into the empty cavities or chambers of the device.

Figure 2C shows attachment of a second cover to the in vivo vascularized MEMS (Micro-Electro-Mechanical Systems) device. This new cover is fabricated to contain internal reservoirs with interconnecting valves and ducts. The internal reservoirs are pre-filled with therapeutic or analytical agents while the valves and ducts are designed to channel these agents into the chamber for in vivo experimental analysis on the transplanted tissues or collection of cells.

Figure 3A shows a polydimethylsiloxane (PDMS) MEMS (Micro-Electro-Mechanical Systems) device or cartridge with a cover that has internal reservoirs, one containing interleukin-1β or TNFα and another containing SDF-1 (CXCR12). The chamber is filled with extracellular matrix (ECM) and angiogenesis growth factors +/- stem cells. The cover is closed and the device is then implanted in vivo.

Figure 3B shows vascularization of the micro-device in vivo as a result of angiogenesis being stimulated by the growth factors. Interleukin-1β or TNFα is released into the chamber to activate endothelial cells to express E-Selectin.

Figure 3C shows release of SDF-1 (CXCL12) into the chamber. Circulating tumor cells first adhere to the activated endothelial cells and then extravasate or migrate into the chamber.

A generic method and design that can be used for creating the vascularized foundation of vascularized laboratory devices in vivo, at different scales of science using biological and/or biocompatible materials is presented. The developmental steps of this method and design are as follows:

1. A pre-fabricated or fabricated structure is made using biological and/or biocompatible materials. This structure has a unique plug-cavity design and consists of at least two parts, a base and a detachable cover. The cavity or cavities are parts of the base while the plug or plugs are parts of the cover. When the cover is in placed, the cavity or cavities may be partially or completely stopped by the plug or plugs. These cavities may be in the form of chambers and ducts.

2. Empty spaces within the pre-fabricated or fabricated structure are then filled with angiogenesis growth factors which may be mixed in a biocompatible solvent or solid, with or without stem cells. If the device is a prefabricated bone mineral block, bone morphogenetic pro-

tein-7 (BMP7) may be added to stimulate development of the bone mineral block into solid bone.

3. The device is surgically implanted in the body.

4. Angiogenesis growth factors stimulate generation of new blood vessels in the device.

5. The cover of the in vivo vascularized device is surgically removed to expose empty spaces previously plugged.

6. Tissues, eg. cancerous tissue, or cells may be transplanted into the empty spaces of the in vivo vascularized device.

7. A second cover is attached to the device and may be fabricated to contain internal reservoirs with interconnecting valves and ducts. The internal reservoirs may be prefilled with therapeutic or analytical agents while the valves and ducts are designed to channel these agents into their respective vascularized chambers for in vivo experimental analysis of transplanted tissues or cells. Alternatively, these reservoirs with experimental agents, interconnecting valves and ducts may be in-built into the non-covered base of the device or the second cover may provide channels that lead to similar structures ex vivo.

One example of creating an in vivo vascularized laboratory device at the macro-level of science, that is devices with features above the micrometer scale, using this generic method and design is a vascularized device designed to analyze bone diseases in vivo (Figures 1A-C). In this instance,

a prefabricated bone device is made of one or many bone mineral blocks filled with angiogenesis growth factors which may be mixed in a biocompatible solvent or solid, with or without stem cells. Bone morphogenetic protein-7 (BMP7) may be added to stimulate development of the bone mineral block into solid bone when implanted in the body. The one or many bone mineral blocks are also designed to have one or many cavities that are filled by one or many reciprocal plugs or stoppers. These plugs or stoppers are parts of a detachable cover for the prefabricated bone device. The detachable cover may be made of biocompatible material like polydimethylsiloxane (PDMS) or titanium. The covered prefabricated bone device is then surgically implanted in the body and after a period develops into a vascularized in vivo device made of bone with a detachable cover. One end of this vascularized device is the arterial end while the other end is venous. The cover is then surgically removed and the empty spaces in the device exposed. These spaces in the device may be filled with pieces of bones that are affected by diseases like leukemia, lymphoma, metastatic solid cancers to the bone etc. A new biocompatible cover may then be fitted over the device converting the open spaces into enclosed vascularized chambers. This new cover may be made of biocompatible material like polydimethylsiloxane (PDMS) and fabricated to contain internal reservoirs with interconnecting valves and ducts. The internal reservoirs may be pre-filled with therapeutic or analytical agents while the valves and ducts are designed to channel these agents into their respective vascularized chambers for in vivo experimental analysis. Alternatively, these reservoirs with experimental agents, interconnecting valves and ducts may be in-built into the non-covered base of the device or the second cover may provide

channels that lead to similar structures ex vivo. (Figures 1A-C)

One example of creating an in vivo vascularized laboratory device at the micro-level of science, that is devices with features at the micrometer scale and below, using this generic method and design is a micro-device designed to analyze tissue responses eg. cancerous tissues or cellular responses to experimental maneuvers in vivo (Figures 2A-C). In this instance, MEMS (Micro-Electro-Mechanical Systems) technology is used to fabricate a device that has interconnecting ducts and chambers and is made using biocompatible materials eg. polydimethylsiloxane (PDMS). This device likewise has a unique detachable cover with reciprocal plug-chamber and plug-duct design that creates spaces in one or many chambers and opens up one or many ducts when the cover is removed. When the cover is in placed, the cover-plugs may stop up some portions or all of their reciprocal chambers and interconnecting ducts. Spaces that are designed to be non-stopped by the cover come together as a main duct that runs directly through the device and intersects with the main chamber. These non-stopped interconnecting spaces of the main duct and main chamber are filled with angiogenesis growth factors which may be mixed in a biocompatible solvent or solid, with or without stem cells. The covered device with impregnated growth factors is then surgically implanted in the body whereupon which angiogenesis is stimulated to occur and after a period results in the generation of new blood vessels in the device. The blood vessels will traverse through the main duct and unstopped spaces of the main chamber from one end to the other. The cover of this vascularized micro-laboratory device in vivo is then surgically re-

moved and spaces in the stopped chambers and interconnecting ducts exposed. Living tissues, eg. cancerous tissue, or cells, can then be transplanted into the vascularized main chambers of the device and kept viable by integrating with the blood vessels in the chamber. A second biocompatible cover may then be fitted over the device converting the open spaces into enclosed chambers and interconnecting ducts once again. This new cover may be made of biocompatible material like polydimethylsiloxane (PDMS) and fabricated to contain internal reservoirs with interconnecting valves and ducts. The internal reservoirs may be pre-filled with therapeutic or analytical agents while the valves and ducts are designed to channel these agents into their respective vascularized chambers for in vivo experimental analysis. Alternatively, these reservoirs with experimental agents, interconnecting valves and ducts may be in-built into the non-covered base of the device or the second cover may provide channels that lead to similar structures ex vivo. (Figures 2A-C)

Both devices described above may be surgically implanted in superficial parts of the body eg. just beneath the skin surface. In conjunction with non-invasive or minimally invasive bio-imaging techniques and fluorescent molecular labelling techniques, experimental end-points eg. cell apoptosis (programmed cell death) of tissues or cells in the different vascularised chambers may be quickly detected after release of experimental agents. This method affords for very early detection and prediction of a particular cancer’s response to different treatment strategies before the main bulk of the patient’s cancer is treated. Hence, a novel method for very early detection of the response of cancerous tissue to various therapeutic agents is made possible.

Another example of creating an in vivo vascularized laboratory device at the micro-level of science is a vascularized device designed to capture circulating tumor cells from the bloodstream of metastatic cancer patients (Figures 3A-C). The chambers of the microdevice may be filled with different kinds of extracellular matrix which may be made from tissue-specific extracts and impregnated with angiogenesis growth factors +/- stem cells. Reservoirs in the cover of the microdevice are pre-filled with endothelium activating factors like interleukin-1β and/or TNFα. A second reservoir is pre-filled with Stromal cell Derived Factor-1 (CXCL12) which is a chemokine. The microdevice is initially implanted in the body and vascularization of the device takes place. The first reservoir containing interleukin-1β and/or TNFα is released to activate the endothelial cells to express E-Selectin. Circulating tumor cells with corresponding ligands will adhere to the endothelial wall. A second reservoir containing SDF-1 (CXCL12) is then release to attract the circulating tumor cells to extravasate and migrate into the chambers. Such a device would be useful for prognosticating future events in the metastatic cancer patient and also useful for studying a poorly understood area of organ-specific metastasis. Once the circulating tumor cells have extravasated in the chambers of the device, they can then be amenable to further in vivo experimentation in the microdevice to find the best drug combination for apoptosis.

- Mirror or reflecting layer at the bottom of the cavity, transparent cover + observation with microscope from outside the body (device is located directly under the skin of the human being)

- other object which may support a measurement (e.g. radioactive substances)

- examples for sensors (pH sensor, O2 sensor, electrical sensors, electro-magnetic sensors, radioactivity sensors)

- examples for supplying and purging the cavity with external rubber tubes

- examples for pumps and valves

- multiple cavities

The following documents are herewith incorporated by reference. They describe in detail how a mineral bone block can successfully be implanted into an animal. This knowledge can be applied to the examples for implanting the vascularized laboratory device of the application.

1. P.H. Warnke, I.N.G. Springer, J. Wiltfang, Y. Acil, H. Eufinger, M. Wehmoller, P.A.J. Russo, H. Bolte, E. Sherry, E. Behrens, H. Terheyden. Growth and transplantation of a custom vascularized bone graft in a man. Lancet 2004;364:766-770

2. H. Terheyden, C Knak, S. Jepsen, S. Palmie, D.R. Rueger. Mandibular reconstruction with a prefabricated vascularized bone graft using recombinant human osteogenic protein-1: an experimental study in miniature pigs. Part I: Prefabrication. Int. J. Oral Maxillofac. Surg. 2001;30: 373-379

3. H. Terheyden, P. Warnke, A. Dunsche, S. Jepsen, W. Brenner, S. Palmie, C. Toth, D.R. Rueger. Mandibular reconstruction with prefabricated vascularized bone grafts using recombinant human osteogenic protein-1: an experimental study in miniature pigs. Part II: Transplantation. Int. J. Oral Maxillofac. Surg 2001;30: 469-478

Further helpful remarks

The subject matter described herein documents a generic method and design that can be used for creating the vascularized foundation of vascularized laboratory devices in vivo at different scales of science using biological and/or biocompatible materials. In parallel, a novel method for very early detection of cancer response to various treatment agents is also described.

This generic method and design consists of filling a prefabricated or fabricated structure with angiogenesis growth factors which may be mixed in a biocompatible solvent or solid, with or without stem cells. Subsequently the device is surgically implanted in the body. The angiogenesis growth factors stimulate generation of new blood vessels in the device in vivo. The vascularized in vivo device can then be used as a base for different experimental purposes. If the device is meant for analysis of blood vessels and/or blood contents in vivo, opto-electronic structures for this purpose may be in-built into the device before implantation.

However, a broader use of the device for a variety of purposes is made possible (achieved) with a unique structural

feature that consists of a detachable cover and reciprocal plug-cavity design that creates spaces in the device to receive transplanted living tissues, eg. cancerous tissue, or cells. A second cover converts these open spaces into enclosed vascularized chambers. The transplanted tissue or cells in each chamber will re-establish connection with the microvascular circulation of the device to remain viable. The second cover can be designed to allow delivery of therapeutic agents into the chambers. These transplanted living tissues or cells are then amenable to experimental analysis in vivo in the chambers and their responses predict closely or exactly that of the original tissue from which they came from.

If the vascularized chambers contain cancerous tissues, different theories of the type of cancer the patient has eg. ‘Xa’, ‘Xb’, ‘Xc’ etc can be used to design specific targeted strategies of treatment. These different treatment strategies can then be tested separately on the cancer tissues in the chambers of the vascularized device which act as controlled environments for experimental analysis. In vivo simulation testing on tissues and cells is thus made possible and the response of the main bulk of cancer can be expected to be very similar when the patient is treated systemically with the chosen therapeutic agent of choice after simulation testing. Because relatively small amounts of therapeutic agents are used in the chambers at any moment in time, these agents are expected to be mainly used up by their mode of action on the transplanted tissues or cells and undergo local metabolism. Even if some of these agents escape into their immediate venous circulation, their relatively small amounts will be diluted further to insignifi-

cant levels. However, vascular microdialysis techniques or continuous veno-venous hemofiltration techniques can be used to remove any escaped drugs at the venous end of the device if necessary.

Because the device may be surgically implanted just beneath the skin surface, it may be supported by a variety of non-invasive or minimally invasive microscopic or bio-imaging techniques, and fluorescent molecular labelling techniques to quickly detect experimental end-points eg. cell apoptosis (programmed cell death) in the different vascularised chambers. This method affords for very early detection and prediction of the cancer's response to different treatment strategies before the main bulk of the patient's cancer is treated systemically. Hence, a novel method for early detection of the response of cancerous tissue to various therapeutic agents is made possible.

Another unique benefit of this method is its ability to test directly for the efficacy of targeted drug therapy i.e. pharmacodynamics without involving bloodstream drug delivery. Hence when the patient begins actual systemic treatment for the main bulk of disease and there is no response, the problem should then lie likely in drug delivery or pharmacokinetics. Even if preliminary testing of therapeutic agents on the cancerous tissues in the vascularized in vivo device is not done and the patient is treated systemically right from the start, this unique method and device can still give us very early detection of cancer response to treatment in conjunction with bio-imaging techniques.

Further Advantages of the subject matter

This generic method and design to create in vivo vascularized laboratory devices originated from the author's search for innovative solutions to treat cancer patients resistant to standard treatments although the subject matter can also be utilized for other biological purposes as described below.

The subject matter provides a tool and a technique to allow transplanted living materials eg. cells, tissues or organs to grow viably in the body in separate implanted compartments. The expression "separate implanted compartments" includes implanted compartments made to locate in or at any part of the body but are not at the beginning of implantation, a natural continuous integral part of that location. This application documents an example method and an example design for doing so by means of vascularizing such compartments in the body and bringing living materials of interest into close proximity with the blood vessels of the implanted device. This approximation maintains the viability of the living material. The advantages of keeping living materials alive in separate implanted compartments *in vivo* are manifold.

1. Living Histology and Physiology:

The subject matter confers new abilities to creating and maintaining a standard row of living materials in the body for observation and study of their dynamic characteristics. In essence, an *in vivo* living and dynamic histology. This would help to better define and refine existing classification systems and nosologies.

The subject matter applies to creating a new method to directly examine dynamic events of living bone marrow histology and physiology. At the present moment, bone marrow histology and physiology is poorly understood due to lack of methods for direct assessment since normal bone marrow is surrounded by thick cortical bone that impedes direct observation and experimental manipulation.

Observation may be performed by:

a) instruments for optical analysis eg. direct microscopic imaging or confocal microscopic imaging or fluorescence imaging or bioluminescence imaging, or intravital videomicroscopy, etc OR

b) instruments that use electro-magnetic radiation like X-Ray, CT Scan, MRI, NMR, Positron Emission Tomography (PET) imaging, thermo imaging, infrared imaging etc OR

c) mass spectrophotometer.

2. Tissue engineering and transplantation:

The subject matter confers new abilities to separation and house living materials in individual vascularized chambers without contact influences, chemical and molecular influences from the surrounding tissue cells in which they are embedded. The same is true if growth and development of the living materials in their own unique vascularized space or chambers is desired. This confers the ability to grow and develop a wide variety of cellular or tissue grafts *in vivo* at any location in preparation for future transplantation in

the same body. Graft rejection from the immune system is not expected to occur unless there is auto-immunity and if present can be detected at the very early stages of viability and growth.

Possible methods of observation are as described in 1) above.

3. Normal tissue and Disease Models:

The subject matter confers new abilities to maintaining viability, growth or development of living tissues that by nature of being *in vivo* and having their own individual separate microenvironments, better replicating the molecular and morphogenic behaviors and microenvironmental interactions of their cellular or tissue counterparts elsewhere in the same body. In essence, more accurate model systems for the study of normal cellular/tissue/organ development and pathogenesis of diseases are created.

Possible methods of observation are as described in 1) above.

4. *In vivo* Experimentation:

The subject matter confers new abilities to performing *in vivo* experimentation and analysis of living materials in similar microenvironments without involving their normal or diseased counterpart elsewhere in the same body. *In vivo* experimentation and analysis can be done with different treatment or analytical agents. The behavioral responses of the treated living materials simulate and predict for the same responses to occur in their normal or diseased counterpart

elsewhere in the same body should the latter be treated similarly.

Perform *in vivo* experimentation and analysis of living materials in different pre-determined microenvironments or extracellular matrices for living materials with migratory capabilities like leukoctyes, circulating tumor cells etc. These cells normally migrate from one microenvironment to another. Their behaviors in different microenvironments can be recreated and tested by this method.

Possible methods of observation are as described in 1) above.

5. Diagnostic and Prognostic studies

The subject matter confers new abilities to better diagnosing and prognosticating the normal or diseased state of health of a human body or of an animal body, through a combination of the aforementioned observation, study, characterization, modeling and *in vivo* experimentation steps.

For example, circulating tumor cells in the blood of cancer patients can be attracted to attach to activated endothelium of the vascularized chamber, and then be attracted to migrate and extravasate pass the endothelial wall of the capillary by chemokines in the chamber contained within different tissue-specific extracellular matrices or tissue-sepecific extracts or living tissues. Detection of this phenomenon prognosticates for different organ-specific metastases in patients with circulating tumor cells in the blood only. A further step would include performing *in vivo* experimentation using different treatment or analytical agents

to better characterize and diagnose the metastatic cells for treatment of the whole body.

Possible methods of observation are as described in 1) above.

6. Early detection of treatment response

The subject matter confers new abilities to detecting early molecular-cellular changes or response of the implanted living tissues when treatment is given to the whole body of a human or animal, via direct or intravital microscopy techniques or other fluorescent bioimaging techniques.

For example, in the treatment of cancer, this application provides a technology that will allow us to detect very early response of different organ-specific metastatic tissues to treatment by directly imaging for apoptosis of the living tissues in the chambers while the patient is being infused with chemotherapy. If apoptosis is not observed in the implanted chambers, the application allows for further *in vivo* experimentation, as afore-described, to search for the next best drug combination to be given to the patient as a whole.

This method is also possible for blood malignancies like leukemia which is more 'fluid' in nature since the application may be in the form of a bone housing the diseased element. To date, no technology exists to directly image for *in vivo* molecular-cellular treatment efficacy when chemotherapy is being administered to the leukemic patient. And no technology exists to allow in vivo experimentation and direct

observation of responses, as afore-described, on diseased bone marrow.

This time factor for early detection of cancer responsiveness is clearly important since the earlier we know that the cancer is not responding to certain drugs, the earlier we can switch treatment strategies to find the right therapeutic drug/s for the patient. Instead of waiting weeks or months later when the patient's functional status has already deteriorated from disease progression and he or she may no longer be able to tolerate further treatment.

Possible methods of observation are as described in 1) above.

7. Direct Pharmacodynamic assessment of treatment efficacy

The subject matter confers new abilities to assessing directly for drug-target interactions or pharmacodynamic efficacy of different treatment agents on their targeted molecules in living cells or tissue. If pharmacodynamic efficacy of a treatment agent is proven by the application and upon treating the patient as a whole with the same agent, there is no response, then problems with inadequate concentrations of therapeutic agent/s reaching the cancer cells in the tumor, i.e. pharmacokinetics should be investigated.

Possible methods of observation are as described in 1) above.

8. Angiogenesis and hematological studies

The subject matter confers new abilities to better understanding the mechanisms of angiogenesis, thrombus formation

and other hematological studies through a combination of the aforementioned observation, study, characterization, modeling and *in vivo* experimentation steps on blood vessels.

Possible methods of observation are as described in 1) above.

Although tissue engineering work has been done in humans and pigs on growing a vascularized bone graft in vivo and transplanting it thereafter to repair bone defects, this is however not a method for creating vascularized laboratory devices in vivo as described by this invention.

To create *in vivo* vascularized laboratory devices designed to analyze blood vessels and/or blood contents *in vivo*, as mentioned above of this patent application, the generic method and design similarly consists of filling a prefabricated or fabricated structure with angiogenesis growth factors which may be mixed in a biocompatible solvent or solid, with or without stem cells. Subsequently the device is surgically implanted in the body (Figure 4A). The angiogenesis growth factors stimulate generation of new blood vessels in the device *in vivo* (Figure 4B). Opto-electronic structures for the analysis of blood contents and/or blood vessels may either be in-built into the device before implantation (Figure 4C) or may be used externally to image the *in vivo* vascularized device (Figure 4D) or some parts of the opto-electronic structures may be *ex vivo* and some parts in-built in the *in vivo* device (Figure 4E).

Possible methods of analyzing comprise – among others – laser examination with or without reflection at the inner part of the structure. The laser light may be brought into the structure with an external laser source which is located outside of the body. A mirror device may be located

in the structure for reflecting the laser light to the outside of the structure.

With regards to the type of blood contents that can be analyzed optically, these include white blood cells and all their sub-types, red blood cells and all their sub-types, platelets and all their sub-types, stem cells and all their sub-types, circulating tumor cells and all their sub-types, circulating endothelial cells and all their sub-types, bacteria, fungus, viruses, parasites, thrombus, blood clot formation, circulating proteins (eg. albumin, globulin, biomarkers etc), circulating hormones (eg. cortisol, thyroid hormone, growth hormone etc), circulating fats and lipids, circulating carbohydrates (eg. glucose), circulating free nucleic acids, circulating antibodies, circulating radio-labeled antibodies, circulating fluorescent-labeled antibodies, circulating chemical/drug-tagged antibodies, circulating radio-contrast agents, circulating drugs and small molecules targeted agents, chemicals, alcohol, bio-chemicals, oxygen, carbon dioxide, carbon monoxide, ions (eg. sodium, potassium, chloride, bicarbonate, urea, creatinine, calcium, phosphorus, magnesium etc), circulating cancer bio-markers (eg. PSA,

CEA, CA 125 etc) etc. Essentially all the components of blood that make up blood whether it is treated blood or untreated blood.

The type of blood vessels that can be analyzed include all types of blood vessels, veins, capillaries, arteries etc.

Claims

1. Method comprising the following steps:
   - extracting a predetermined part of the body,
   - implanting the extracted part of the body at/in another location in the body,
   - subjecting the implanted part of the body to a predetermined treatment,
   - observing the treated part of the body.

2. Method according to claim 1, comprising a further step of determining the outcome of the treatment.

3. Method according to one of the aforementioned claims, wherein the step of observing the treated part of the body includes a step of purging liquid from the treated part of the body and a step of measuring predetermined characteristics of the purged liquid.

4. Method according to one of the aforementioned claims, wherein the step of observing the treated part of the body includes an optical verification or a verification with electro-magnetic radiation.

5. Method according to one of the aforementioned claims, wherein before the step of implanting the extracted part of the body at/in another location in the body, there is provided a step of implanting a receptacle device at the location of the body, the receptacle device being formed to receive the extracted part of the body.

6. Method according to claim 5, wherein the receptacle device is left such a time within the body that at least one contact area for receiving the extracted part of the body is vascularized at the time of implanting the extracted part of the body into the receptacle device.

7. Method according to claim 5 or claim 6, wherein at least one part of the receptacle device is replaced by a covering means at the time at the time of implanting the extracted part of the body into the receptacle device.

8. Method according to one of claims 5 to 7, wherein the step of implanting the receptacle device at the location of the body is done such that the receptacle is covered fully under a skin portion of the body.

9. Method according to one of claims 5 to 7, wherein the step of implanting the receptacle device at the location of the body is done such that the receptacle is partially underneath a skin portion of the body, partially protruding from the body.

10. Method for treating an animal or a human being, the method comprising the following steps:
- performing the steps of testing the effectiveness of two or more treatments on two or more parts of a body of an animal or of a human being at the same time with the steps according to one or more of the aforementioned claims,
- selecting the most effective treatment, and

- treating the body of the animal or human being according to the selected treatment.

11. Method for treating an animal or a human being according to claim 10, wherein during the step of treating the body of the animal or human being according to the selected treatment the steps according to one or more of claims 1 to 9 are continued.

11. Device for receiving a part of a body of an animal or of a human being, the device comprising the following features:
- a block device of biocompatible material,
- a detachable covering means of biocompatible material,
- at least one receiving area provided by the block device and the covering means,

wherein at least the block device comprises duct means extending between at least one outer surface area of the block device and the at least one receiving area.

12. Device according to claim 11,
wherein the biocompatible material comprises bone mineral material.

13. Device according to claims 12,
wherein at least part of the block device comprises bone morphogenetic protein-7 (BMP7).

14. Device according to claim 11,
wherein the biocompatible material comprises titanium or polydimethylsiloxane (PDMS) material .

15. Device according to one of claims 11 to 14, wherein at least part of the block device comprises angiogenesis growth factors.

16. Device according to claim 15, wherein the angiogenesis growth factors are mixed in a biocompatible solvent.

17. Device according to claim 15, wherein the angiogenesis growth factors are solid.

18. Device according to one of claims 11 to 17, wherein at least part of the block device comprises stem cells.

19. Device according to one of claims 11 to 18, wherein two or more of the at least one receiving areas are provided.

20. Device according to one of claims 11 to 18, wherein the at least one receiving area comprises a detachable filling means.

21. Device according to claim 20, wherein the filling means is a part of the covering means.

22. Covering means for use with a block device, the covering means being mechanically compatible with the block device.

23. Covering means according to claim 22, wherein the covering means comprises biocompatible material.

24. Covering means according to claim 23, wherein the biocompatible material comprises bone mineral material.

25. Covering means according to claim 24, wherein at least part of the covering means comprises bone morphogenetic protein-7 (BMP7).

26. Covering means according to claim 23, wherein the biocompatible material comprises titanium or polydimethylsiloxane (PDMS) material .

27. Covering means according to one of claims 22 to 26, wherein at least part of the covering device comprises angiogenesis growth factors.

28. Covering means according to claim 27, wherein the angiogenesis growth factors are mixed in a biocompatible solvent.

29. Covering means according to claim 27, wherein the angiogenesis growth factors are solid.

30. Covering means according to one of claims 22 to 29, wherein at least part of the covering means comprises stem cells.

31. Covering means according to one of claims 22 to 30,

wherein two or more receiving areas are provided.

32. Covering means according to one of claims 22 to 30, wherein at least one internal reservoir is provided in the vicinity of at least one receiving area.

33. Covering means according to 32, wherein at least one internal reservoir comprises at least one an duct extending between the reservoir and the receiving area.

34. Covering means according to claim 32 or claim 33, wherein the duct comprises an operable valve for at least partly opening or at least partly closing the duct.

35. Covering means according to claim 34, wherein the valve is operable by external means.

36. Covering means according to one of the claims 32 to 35, wherein the duct comprises an operable pump.

37. Covering means according to claim 36, wherein the pump is operable by external means.

38. Covering means according to one of claims 32 to 37, wherein the reservoir is pre-filled with agents.

39. Block device for use with a covering means, the covering means being mechanically compatible with the block device.

40. Block device according to claim 39,

wherein the block device comprises biocompatible material.

41. Block device according to claim 40, wherein the biocompatible material comprises bone mineral material.

42. Block device according to claim 41, wherein at least part of the block device comprises bone morphogenetic protein-7 (BMP7).

43. Covering means according to claim 40, wherein the biocompatible material comprises titanium or polydimethylsiloxane (PDMS) material .

44. Block device according to one of claims 39 to 43, wherein at least part of the block device comprises angiogenesis growth factors.

45. Block device according to claim 44, wherein the angiogenesis growth factors are mixed in a biocompatible solvent.

46. Block device according to claim 44, wherein the angiogenesis growth factors are solid.

47. Block device according to one of claims 39 to 46, wherein at least part of the block device comprises stem cells.

48. Block device according to one of claims 39 to 47, wherein two or more receiving areas are provided.

49. Block device according to one of claims 39 to 48, wherein at least one internal reservoir is provided in the vicinity of at least one receiving area.

50. Block device according to 49, wherein at least one internal reservoir comprises at least one an duct extending between the reservoir and the receiving area.

51. Block device according to claim 49 or claim 50, wherein the duct comprises an operable valve for at least partly opening or at least partly closing the duct.

52. Block device according to claim 51, wherein the valve is operable by external means.

53. Covering means according to one of the claims 50 to 52, wherein the duct comprises an operable pump.

54. Covering means according to claim 53, wherein the pump is operable by external means.

55. Block device according to one of claims 49 to 54, wherein the reservoir is pre-filled with agents.

56. Method comprising the following steps:
- implanting a receptacle device at a predetermined location of the body, the receptacle device being formed to receive at least one predetermined part of the body,

- waiting a predetermined time for the predetermined part of the body being received in the receptacle device,
- evaluating the predetermined part of the body being received in the receptacle device.

57. Method according to claim 56, wherein the receptacle device is left such a time within the body that at least one contact area for receiving the extracted part of the body is vascularized at the time of implanting the extracted part of the body into the receptacle device.

58. Method according to claim 56 or claim 57, wherein at least one part of the receptacle device is replaced by a covering means before the step of waiting a predetermined time for the predetermined part of the body being received in the receptacle device.

59. Method according to one of claims 56 to 58, wherein at least one part of the receptacle device is replaced by a covering means after the step of waiting a predetermined time for the predetermined part of the body being received in the receptacle device and before the step of evaluating the predetermined part of the body being received in the receptacle device.

60. Method according to one of claims 56 to 59, wherein the step of implanting the receptacle device at the location of the body is done such that the receptacle is covered fully under a skin portion of the body.

61. Method according to one of claims 56 to 60, wherein the step of implanting the receptacle device at the location of the body is done such that the receptacle is partially underneath a skin portion of the body, partially protruding from the body.

62. Method according to one of the aforementioned claims, wherein the step of evaluating the predetermined part of the body being received in the receptacle device includes a step of purging liquid from the treated part of the body and a step of measuring predetermined characteristics of the purged liquid.

63. Method according to one of the aforementioned claims, wherein the step of evaluating the predetermined part of the body being received in the receptacle device includes an optical analysis and verification or an analysis and verification with electro-magnetic radiation.

64. Method for treating an animal or a human being, the method comprising the following steps:

- performing the steps of testing the effectiveness of two or more treatments on two or more parts of a body of an animal or of a human being at the same time with the steps according to one or more of the aforementioned claims,
- selecting the most effective treatment, and
- treating the body of the animal or human being according to the selected treatment.

65. Device for receiving a part of a body of an animal or of a human being, the device comprising the following features:
- a block device of biocompatible material,
- at least one receiving area provided by the block device,

wherein the block device comprises duct means extending between at least one outer surface area of the block device and the at least one receiving area.

66. Device according to claim 65, wherein a detachable covering means of biocompatible material is provided on the block device.

67. Device according to claim 66, wherein at least one receiving area provided by the covering means.

68. Device according to one of claims 65 to 67, wherein the biocompatible material comprises bone mineral material.

69. Device according to claims 68, wherein at least part of the block device comprises bone morphogenetic protein-7 (BMP7).

70. Device according to one of claims 65 to 67, wherein the biocompatible material comprises titanium or polydimethylsiloxane (PDMS) material.

71. Device according to one of claims 65 to 70, wherein at least part of the block device comprises angiogenesis growth factors.

72. Device according to claim 71,
wherein the angiogenesis growth factors are mixed in a biocompatible solvent.

73. Device according to claim 72,
wherein the angiogenesis growth factors are solid.

74. Device according to one of claims 65 to 73,
wherein at least part of the block device comprises stem cells.

75. Device according to one of claims 65 to 74,
wherein two or more of the at least one receiving areas are provided.

76. Covering means for use with a block device according to one of claims 65 to 75, the covering means being mechanically compatible with the block device.

77. Covering means according to claim 76,
wherein the covering means comprises biocompatible material.

78. Covering means according to claim 77,
wherein the biocompatible material comprises bone mineral material.

79. Covering means according to claim 78,
wherein at least part of the covering means comprises bone morphogenetic protein-7 (BMP7).

80. Covering means according to claim 77, wherein the biocompatible material comprises titanium or polydimethylsiloxane (PDMS) material .

81. Covering means according to one of claims 76 to 80, wherein at least part of the covering means comprises angiogenesis growth factors.

82. Covering means according to claim 81, wherein the angiogenesis growth factors are mixed in a biocompatible solvent.

83. Covering means according to claim 81, wherein the angiogenesis growth factors are solid.

84. Covering means according to one of claims 76 to 83, wherein at least part of the covering means comprises stem cells.

85. Covering means according to one of claims 76 to 84, wherein two or more receiving areas are provided.

86. Covering means according to one of claims 76 to 85, wherein at least one internal reservoir is provided in the vicinity of at least one receiving area.

87. Covering means according to 86, wherein at least one internal reservoir comprises at least one an duct extending between the reservoir and the receiving area.

88. Covering means according to claim 87,

wherein the duct comprises an operable valve for at least partly opening or at least partly closing the duct.

89. Covering means according to claim 88, wherein the valve is operable by external means.

90. Covering means according to one of the claims 87 to 89, wherein the duct comprises an operable pump.

91. Covering means according to claim 90, wherein the pump is operable by external means.

92. Covering means according to one of claims 86 to 91, wherein the reservoir is pre-filled with agents.

93. Block device for use with a covering means according to one of the claims 76 to 92, the block device being mechanically compatible with the covering means.

94. Block device according to claim 93, wherein the block device comprises biocompatible material.

95. Block device according to claim 94, wherein the biocompatible material comprises bone mineral material.

96. Block device according to claim 95, wherein at least part of the block device comprises bone morphogenetic protein-7 (BMP7).

97. Block device according to claim 94, wherein the biocompatible material comprises titanium or polydimethylsiloxane (PDMS) material.

98. Block device according to one of claims 93 to 97, wherein at least part of the block device comprises angiogenesis growth factors.

99. Block device according to claim 98, wherein the angiogenesis growth factors are mixed in a biocompatible solvent.

100. Block device according to claim 99, wherein the angiogenesis growth factors are solid.

101. Block device according to one of claims 93 to 100, wherein at least part of the block device comprises stem cells.

102. Block device according to one of claims 93 to 101, wherein two or more receiving areas are provided.

103. Block device according to one of claims 93 to 102, wherein at least one internal reservoir is provided in the vicinity of at least one receiving area.

104. Block device according to 103, wherein at least one internal reservoir comprises at least one an duct extending between the reservoir and the receiving area.

105. Block device according to claim 104,

wherein the duct comprises an operable valve for at least partly opening or at least partly closing the duct.

106. Block device according to claim 105, wherein the valve is operable by external (remote) means.

107. Block device according to one of the claims 105 to 106, wherein the duct comprises an operable pump.

108. Block device according to claim 107, wherein the pump is operable by external means.

109. Block device according to one of claims 104 to 108, wherein the reservoir is pre-filled with agents.

110. Method comprising the following steps:

- implanting a receptacle device at a predetermined location of a body,
- waiting a predetermined time for the receptacle device to be vascularised,
- analyzing the blood stream through the vascularised receptacle device with optical means and / or with electromagnetical radiation.

111. Method of claim 110, wherein the analysis is done from outside of the body.