

Coated medical device and method of coating a medical device to reduce, fibrosis and capsule formation.

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FIELD OF THE INVENTION

The present invention relates to a coating technology modulating cell adhesion on the surface of medical devices. The coating prevents capsule formation and decreases fibrosis induced by foreign bodies such as medical devices.

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BACKGROUND OF THE INVENTION

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Medical devices in contact with living cells and tissues induce a foreign body reaction due to their physical and chemical properties. This process results in a capsule formation around the implant that often contracts and results in malfunctioning of the device and clinically relevant complications such as pain and dysmorphism of the patient that ultimately require additional surgical operations.

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The reaction of cells to a foreign material such as for example a silicone breast and aesthetic implant, a gastric band, a dental implant, an orthopedic implant, hearth heart valve, etc., which cannot be phagocytated, enzymatically digested or otherwise eliminated, is the formation of fibrotic capsule around it.

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It has been reported by Prantl L., and al. (Clinical and morphological conditions in capsular contracture formed around silicone breast implants, *Plast Reconstr Surg* 2007, 120:275-284) that in up to 20-30% of implanted prosthesis develop capsule formation. The capsule formation is excessive and leads to clinically relevant, painful contractures around the device. Patients with excessive capsular formation need to receive a second operation to remove the capsule around the device which considerable increases in the morbidity and costs. This process significantly shortens the lifespan of the device.

This capsule is the result of a chronic inflammatory process around the material that resolves only after the formation of the capsule itself.

Myofibroblasts play a main role in capsule formation and contraction in healing tissues. The capsule itself is deposited and contracted by myofibroblasts. In the wound healing process, these highly active cells proliferate and growth to occupy tissue defects and replaces them with a scar. Around the implant, myofibroblast deposit collagen fibers around the foreign material and eventually contract it. This reaction produces capsular contraction.

The problem of capsule formation has also been discussed in patent literature. In US 4,772,285 a collagen coated soft tissue prosthesis is described for reducing capsule formation. While this patent proposes a strategy to decrease capsule formation, no mechanism is provided to effect myofibroblast formation. Further the clinical evidence is lacking.

US 4,955,907; 4,731,081; 5,571,183; 5,207,709; 5,354,338; 4,428,082 and 4,298,998 also propose solutions to avoid or diminish capsule formation.

- 5 All these documents have several common denominators which have the potential of making them unsuitable for resolving this problem in human beings.

10 For example US 4,298,998 disclose causing a capsule to form at a predetermined, controlled distance from the surface of the implant, thus resulting in the same capsule but at a different location. The end result clinically appears to be a hard capsule for the patient and not resolving the problem.

15 Similarly, the implant described in US 5,207,709 includes a plurality of fine projections extending from the outer surface arrayed in a basket weave-like, herringbone-like, or other suitable pattern to create a sinuous path for collagen formation around the implanted device. It appears that this implant actually creates or invites collagen formation
20 again in another location around the implant and again therefore is not resolving the problem.

Still other patents relate to the implant being surrounded by a medical grade elastomer or as described in US 4,944,749 a viscous gel coating
25 with the membranes constructed of a suitable material such as medical grade silicone rubber, which does not react with human tissue. The outer membrane contains an amount of viscous gel, for example a silicone rubber gel of medical grade silicone.

It appears in the end that this patent still has a silicone tissue interface that has accounted for problems.

- 5 US 4,610,690 is directed to an implant with a lubricious layer of an acrylamide polymer radiation bonded to at least one wall surface of a silicone shell or bag. Potential long-term effects in human beings of an acrylamide polymer interface are not discussed.
- 10 All these aforementioned patents continue to have unnatural chemicals as interface with human tissue, which is exactly what patients do not want in their body and what usually causes problems.

- 15 In US 4,995,882 an organic fill solution is proposed to solve the problem. The implant is proposed the use a triglyceride fill substance such as peanut oil or sunflower seed oil as a filling substance.

- Although some implants of this kind were implanted in Europe, they were never authorized for implantation in the United States and were
20 subsequently taken off the market worldwide because of various problems.

- Although many strategies have been developed to reduce capsule formation, from modifications of the surface of the implants to chemical
25 coatings, only mixed results have been reported and, with the increase in the demand for implantable devices, the clinical problem is on the rise.

SUMMARY OF THE INVENTION

It is therefore an object of the invention to provide a coating of a
5 medical device and a method to produce it with which the fibrosis and
capsule contraction can be further diminished or even avoided.

This can be achieved by a medical device wherein a surface of the
medical device is coated with cell-adhesive proteins deposited in a
10 matrix of islets with specific size, area and distribution, object of this
invention.

This coated surface, which is supposed to come in contact with living
cells and tissues to modulate cell adhesion is composed from two
15 specific regions:

1. Area (islets) where cell (tissue) can specifically attach (coated part),
and
2. Other region where cell (tissue) cannot specifically attach (non coated
part).

20 This invention relates in general to a method and device for guiding
cellular adhesion on medical devices. The invention relates to a method
comprising protein islets to coat devices (implantable and external) in
contact with any cell and tissue of the body.

25 Specifically, the invention contemplates the use of such technique in
combination with devices implanted or externally applied to the body.

This proposal outlines a novel strategy based on islands of proteins to decrease the formation of fibrosis reaction and contraction around medical devices.

- 5 According to a preferred embodiment of the invention the medical device comprises silicone as a material of the medical device.

Other preferred embodiments include the use of plastic, metal and/or collagen as a material of the medical device.

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According to one embodiment of the invention the medical device according to the invention comprises islets of proteins with uniform geometric shapes.

- 15 Another possibility would be the use of different geometric shapes.

Generally, to reduce the myofibroblast differentiation and fibrosis, the area of the single islets is less than $12 \mu\text{m}^2$.

- 20 The topography of islets that best reduces fibrosis is composed of single islets, wherein the islets have preferably a length that is $<6 \mu\text{m}$, a width that is $<2 \mu\text{m}$ and distance between them that is $<6 \mu\text{m}$

- 25 In a preferred embodiment of the invention the medical device further comprises an additional substrate to facilitate the transfer of the islets of proteins.

The substrate which is preferably applied to the medical device before coating same with proteins could be silicone, plastic, bio resistant materials, etc..

- 5 Further the invention describes a method of coating a medical device, wherein the medical device is coated with cell-adhesive proteins in form of single islets.

10 As already mentioned it could be in some embodiments of advantage if the medical device is coated by a substrate before being coated by the proteins.

15 According to one embodiment of the invention the proteins are applied to the medical device by a stencil or mask (a template with holes of the size and distribution of the islets).

20 For applying the proteins according to another embodiment the stencil or mask could be brought in contact with the surface of the medical device and the proteins are transferred to the surface through holes of the stencil.

25 The fixing of the proteins to the medical device could be done by every possibility known from the art. As an example, it should be mentioned covalent binding, electro deposition or precipitation of proteins on the medical device and/or the substrate.

The medical device as described can be used for example for breast implants, tissue expanders, inflatable bumps, implants, transplants,

prosthesis, insulin pumps, drug delivery systems, cardiovascular devices, skin substitutes, wound dressings and/or tubes.

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DETAILED DESCRIPTION OF THE INVENTION

These and other objects, features, aspects and advantages of the present invention will become more apparent from the following detailed
10 description of the present invention when taken in conjunction with the accompanying drawings.

Figure 1 shows a medical device before and after being coated according to one embodiment of the invention; and

15 Figure 2 shows examples of islet shapes according to a preferred embodiment of the invention.

The invention describes a new method of micro-deposition of cell-adhesive proteins and molecules onto the surface of medical devices,
20 such as, but not limited to highly deformable and elastic substrates (such as, but not limited to silicone), Titanium, Plastic, Polyurethane and generally all materials used for medical devices and implants.

The micro-deposited islets of proteins guide cell adhesion on medical
25 devices with the objective to reduce the fibrotic reaction of the cells and tissues in contact with the device.

As shown in Figure 1 according to an embodiment of the invention a microperforated stencil or mask is used to transfer proteins to coat a medical device. 1. Deposition of the proteins and molecules is in the form of specific islets. 2. Protein islets include any possible geometrical shape and spatial organization and individual area. Protein islets (2) are deposited to modulate cell and tissue adhesion to medical devices (1).

The distance between the islets may vary from 1 to 50 μm . The area of the single islets being less than 12 μm^2 .

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The distribution of protein islets according to a preferred embodiment of the invention to best reduce fibrosis includes single islets, wherein the islets have a length that is $<6 \mu\text{m}$, a width that is $<2 \mu\text{m}$ and distance between them that is $<6 \mu\text{m}$.

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In another embodiment, deposited islets could have any geometrical shape. Examples to which the invention is not limited are illustrated in Figure 2.

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The mask or a stencil to transfer the islets is micro fabricated using technology as for example photolithography, dry and wet etching, laser cutting.

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As type of mask or stencil should be mentioned soft stencils made from silicone and flexible polymers and hard stencils from silicon, hard polymer and metal.

To deposit proteins onto medical device as for example an implant surface, the stencil is first brought in conformal contact with the surface and then the proteins are transferred on the surface through the micro-
5 holes of the stencil by covalent binding using 3-aminopropyltriethoxysilane (APTES) and glutaraldehyde or formaldehyde. After the crosslinking of proteins, the stencil is removed and the pattern remains on the implant surface.

10 Another possible method is electro deposition or precipitation of proteins on implant or medical device surface through the micro-holes of stencil or mask. These possibilities are just examples and should not limit the invention to this approach of deposition.

15 Our results in vitro and in vivo illustrate the importance of the size of the islets in reducing fibrosis and contraction around implants proving the relevance of this invention. We found that the main mechanism responsible for limiting the differentiation of human dermal fibroblasts in myofibroblasts (the main cell responsible for fibrosis and contraction) is
20 the area of adhesion.

In our experiments, the islets represent areas of adhesion (focal adhesions) for the cells and dimensions of the islets of a length that is
25 <6 μm , a width that is <2 μm and distance between them that is <6 μm impaired the formation of myofibroblasts (Figure 3).

The specific islet size and distribution with a length $<6\ \mu\text{m}$, a width $<2\ \mu\text{m}$ and distance between them $<6\ \mu\text{m}$ does not allow fibroblasts to exert forces on the surface where they attach and become myofibroblasts (the main cell responsible for fibrosis and contraction).

- 5 In vitro, we showed that this specific size and distribution of proteins reduced 10-fold the differentiation of human dermal fibroblasts to myofibroblasts compared to devices coated with other size and distribution of proteins (Figure 4). The deposition of islets of higher size allowed the differentiation of fibroblasts in myofibroblasts. These later
10 cells were seen in high percentage (up to 20%) when the surface was coated with larger islets than the specific ones provided by this invention (Figure 5).

- In vivo, silicone pads (1x1 cm) covalently coated with a stencil or mask,
15 as described in the methods, on both side with protein islets with a length $<6\ \mu\text{m}$, a width $<2\ \mu\text{m}$ and distance between them $<6\ \mu\text{m}$, were inserted in subcutaneous pockets, in female Wistar rats (250-350 g). On the scapular region of the dorsum of these animals, 4 coated silicone pads were placed. Each animal received four implants: two implants
20 coated with islets with a length $<6\ \mu\text{m}$, a width $<2\ \mu\text{m}$ and distance between them $<6\ \mu\text{m}$; and two non coated silicone implants, alternating the location on successive animals. Results at 6 months show a 3-fold decrease in capsule formation around implants coated with islets of proteins with a length $<6\ \mu\text{m}$, a width $<2\ \mu\text{m}$ and distance between
25 them $<6\ \mu\text{m}$ (Figure 6).

In vitro and in vivo results show that the transformation of fibroblasts into myofibroblasts is crucial in the development of fibrosis and capsule

contraction around medical implants and underline the importance of this invention specifically limiting this event.

- 5 The optimized protein islets deposition with e.g. a length $<6\ \mu\text{m}$, a width $<2\ \mu\text{m}$ and distance between them $<6\ \mu\text{m}$ can be applied to any medical device such as, but not limited to:
- Silicone breast implants
 - Tissue expanders and inflatable pumps
 - 10 • Bone, and cartilage and orthopaedic implants
 - Tendon, nerve, and ligament transplants, substitutes and implants
 - Implantable pumps, such as insuline pumps and drug delivery systems
 - Cardiovascular devices, such as pace makers, vascular prosthesis,
 - 15 heart valves, vascular stents
 - Skin substitutes and cell scaffolds
 - Wound dressings, including dressings and wound interfaces connected to a vacuum (negative pressure dressings)
 - Acoustic waves (such as shockwave therapy)
 - 20 • Ear, throat, nose and eye implants
 - Brain, central and peripheral nervous system implants and prosthesis
 - Tubes, connecting tubes, drainage tube systems

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Claims

1. Coating for a medical device comprising cell-adhesive proteins having the ability to reduce fibrous reaction, said coating being in the form of separate islets having an individual area which is less than $12\text{ }\mu\text{m}^2$ and wherein the distance between the islets is less than $50\text{ }\mu\text{m}$.
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2. Coating according to claim 1 wherein the distance between the islets is less than $6\text{ }\mu\text{m}$.
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3. Coating according to claim 1 or 2 wherein the distance between the islets is more than $1\text{ }\mu\text{m}$.
4. Coating according to one of the previous claims wherein the cell-adhesive proteins are composed of collagen.
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5. Coating according to one of the previous claims 1 to 3 wherein the cell-adhesive proteins are composed of fibronectin, vitronectin alone or in combination.
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6. Coating according to one of the previous claims wherein the islets have a uniform geometrical shape.
7. Coating according to one of the previous claims 1 to 5 wherein the islets have a non-uniform geometrical shape.
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8. Medical device comprising a coating as defined in one of the previous claims.

5 9. Medical device according to claim 8 comprising an additional substrate, which is adapted to facilitate the transfer of the islets of proteins.

10 10. Process for fixing a coating as defined in one of the previous claims on a medical device, said process comprising a step during which the proteins are applied/transferred by a stencil.

15 11. Process according to claim 1 wherein said the stencil is brought in contact with the surface of the medical device and the proteins are fixed to the surface through holes in the stencil.

12. Stencil or mask to be used with the process of claim 10 or 11, said stencil or mask being obtained by photolithography, dry or wet etching, laser cutting.

20 13. Stencil according to claim 12 being soft and being made from silicone and flexible polymers.

25 14. Stencil according to claim 12 being hard and being made from silicon, hard polymers and metal.

15. Use of a coating as defined in any of claims 1 to 7 comprising islets with a length which is less than 6 μm and a width which is less than 2 μm , as a liquid solution to reduce fibrosis.

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