**Abstract:** The invention described herein is applicable in the field of medical health. In particular, the present invention is applicable in any type of surgery that requires the tissue regeneration in patients. Specifically, the object of this application is to provide a very new device for the regeneration of tissues that consist in collagen membranes that originate from the intestinal submucosa, and are reinforced with a titanium mesh in such a way that the two materials are integrated to form the device. This tissue regenerative device can have variations in its thickness, as much in the biological component produced by the collagen membranes originating from the intestinal submucosa as in the alloplastic component made of titanium. The new product of the invention described herein can be utilized in an effective and simple manner in diverse surgical applications having to do with the regeneration of diverse tissues of a patient, given that it contributes to the ordered, rapid and efficient healing process and helps to replace parts of the body which have suffered grave traumas due to illnesses or accidents, returning to them the highest percentage of lost function and esthetic. As well, the device of the present invention provides a new option for the remodeling and reconstruction of tissues given its structure and composition. Additionally, the present invention provides a procedure for the preparation of the new device, characterized by specific stages and conditions necessary to obtain it.
TISSUES REGENERATOR DEVICE BASED ON COLLAGEN AND PROCESS FOR THE PRODUCTION OF THIS DEVICE

The present invention is related with an innovative tissue regenerator system, with a wide range of clinical applications: this device is essentially made with an intestinal submucose reinforced with a titanium mesh, in such way that it integrates in one structure different variations of thickness and configurations of the components; making it a versatile and simple to use promoter of faster, organized and more effective healing processes. 

1. STATE OF THE ART

Currently, reconstructive surgery faces the problem of finding uncontrolled healing processes that leave undesired results in many procedures. Despite the quality of the result this is always affected in one way or another. The membranes used for the guided tissue regeneration technique have shown to be effective in the healing process arrangement.

The small intestinal submucose has been studied for several years, i.e. (international application serial NO. PCT/US97/23006, filed Dec. 10, 1997,designating USA Provisional Application serial No. 60/032,679, filed Dec. 10, 1996).

Within the area of general reconstructive surgery, where the problem rests in the creation or recuperation of insufficient or inexistent tissues, there are great obstacles that often times reduce the quality of the results. Surgeons always to some degree have their hands tied because the healing process is almost in its entirety dependant on a biological process inherent to each patient. Such a
difficulty means that morbidity increases and the quality of the reconstruction is reduced in many cases.

It is for this reason that the implementation of different technologies have been suggested for the development of substitutes that help to achieve an orderly, rapid and efficient healing process, that contributes to replacing parts of the body which have suffered grave traumas due to illnesses or accidents, returning to them the highest percentage of lost function and esthetics.

Recently, researchers have worked with polymeric materials that have certain biomechanical characteristics (for example, compressive forces resistance), but their biocompatibility qualities have not been satisfactory and their use in guided tissue regeneration remains in question.

Today despite the variety of alternatives that have plastic, ceramic, metallic and biological materials, the medical community still lacks a NON-immunogenic material, having a regenerative capacity that displays a high resistance to compressive forces without becoming deformed and which can be used to repair bones and other functional structures.

Consequently, it is clear that in this state of the art, still there is a need for an innovative alternative that can provide an efficient and simple tissue regenerator device with appropriate biomechanical characteristics and a highly effective healing capacity.

2. FIGURES DESCRIPTION

The tissular regenerator device and the method for this invention is better and more simple understood by checking the list of figures as follows:

Figure number 1, shows a transverse view of the yeyunum (Small intestine).
**Figure number 2**, shows a schematic representation of a multilayered membrane composed by multiple single layers of collagen in different orientations.

**Figure number 3**, shows the porcine intestinal submucose isolation and purification process.

**Figure number 4**, shows a conventional titanium mesh.

**Figure number 5**, shows the collagen incorporation phase of the intestinal submucose to the titanium mesh.

**Figure number 6**, shows three different titanium mesh designs, during the collagen incorporation phase.

**Figure number 7**. Shows the first embodiment of the final product of this invention in a 3D configuration.

**Figure number 8**, shows a second embodiment of the final product of this invention in a 3D configuration.

**Figure number 9**, shows a third embodiment of the final product of this invention in a 3D configuration.

**Figure number 10**, shows a fourth embodiment of the final product of this invention in a 3D configuration.

### 3. DETAILED DESCRIPTION OF THE INVENTION

In order to overcome the disadvantages and inconveniences described earlier for the systems and mechanisms employed conventionally for the regeneration of tissues, the present invention provides a new device that combines the
biological properties of collagen originating from the small intestinal submucose of mammals and the alloplastic advantages of titanium meshes, as well as its preparation method.

Although the small intestinal submucose biomechanically exhibits interesting properties "per se," such as its elasticity and the size of the pores, which translates into versatility and ease of manipulation in a clinical sense, nevertheless, this material lacks the ability to be molded, which makes its incapable of reproducing 3-D geometric shapes. This limits its applications in situations where this characteristic is required.

The object of the present application is to present the development of new collagen membranes originating from the small intestinal submucose reinforced with a titanium mesh, integrating the two materials to make up the device of the present invention which can have variations in its thickness, as much in the biological component produced by the collagen membranes originating from the small intestinal submucose as in the alloplastic component made of titanium. In this way, the product obtained through the procedure of the present invention can be used in general in reconstructive surgeries, for example in oral and maxillofacial surgery to perform guided bone regeneration techniques to reconstruct dento alveolar bone of the maxilla and mandible; in plastic and reconstructive surgery, to regenerate bone defects in the face and cranium; in general surgery, as a reinforcement of the abdominal walls for the handling of eventrations and hernias of different sizes; in spinal surgery and neurosurgery, as a protective material for intervertebral discs and implants. These membranes provide an option for the remodeling and reconstruction of tissue given their structure and composition. The manufacturing process is simple and involves the superposition of several layers of a matrix of purified collagen that cover a flat structure of titanium of different densities and mesh designs, making it versatile in its clinical applications. The titanium structure allows the compound to be molded to imitate and maintain tri-dimensional shapes acting as a container, that can be set and immobilized in a stable form. Its biological
component made up of the submucose acts as a barrier and as tissue regeneration material.

Consequently, in a first embodiment, the present invention provides a regeneration of tissues system characterized because it includes collagen membranes originating from the intestinal submucose and a titanium mesh of diverse geometric configurations, in such a way as it is integrated into a titanium-collagen structure.

In an embodiment, the system of regeneration of tissues of the present invention is characterized because of the collagen originating from the intestinal submucose is of a warm-blooded vertebræ.

In a preferred embodiment, the system of tissue regeneration of the present invention is characterized because the collagen originating from the intestinal submucose originates from a porcine.

In an embodiment, the regeneration of materials device such as that from the present invention is characterized because it has a thickness that varies between 0.1 and 1.5 mm and it has a size that varies between 1x1 cm to 25x25 cm.

In an even more preferred embodiment, the tissue regeneration device like that of the present invention is characterized because it has a thickness that varies between 0.3 and 1.2 mm and it has a size that varies between 5x5 cm to 20x20 cm.

In an even more preferred embodiment, the tissue regeneration device like that of the present invention is characterized because it has a thickness that varies between 0.5 and 1.0 mm and it has a size that varies between 10x10 cm to 15x15 cm.
In another embodiment, the tissue regeneration device like that of the present invention is characterized because the titanium mesh has orifices that vary between 1.0 and 2.3 mm.

In another preferred embodiment, the tissue regeneration device like that of the present invention is characterized because the titanium mesh has orifices of 1.0 mm.

In another preferred embodiment, the tissue regeneration device like that of the present invention is characterized because the titanium mesh has orifices of 1.5mm.

In another preferred embodiment, the tissue regeneration device like that of the present invention is characterized because the titanium mesh has orifices of 2.0 mm.

In another preferred embodiment, the tissue regeneration device like that of the present invention is characterized because the titanium mesh has orifices of 2.3 mm.

In another preferred embodiment, the tissue regeneration device like that of the present invention is characterized because the titanium mesh is flat with the capacity to be molded.

In another preferred embodiment, the tissue regeneration device like that of the present invention is characterized because the titanium mesh has diverse 3-D shapes.

In another preferred embodiment, the tissue regeneration device like that of the present invention is characterized because the titanium mesh has Y, H, rectangular, squared and half-moon shapes.
In another embodiment, the tissue regeneration device like that of the present invention is characterized because it can adhere from one layer of collagen to multiple layers of collagen.

In another preferred embodiment, the tissue regeneration device like that of the present invention is characterized because it can adhere from one layer of collagen to six layers of collagen.

In another embodiment, the tissue regeneration device like that of the present invention is characterized because it can adhere from two layers of collagen to four layers of collagen.

Another objective in the present invention is to include the preparation method for the titanium-collagen tissue regeneration device for the present invention. In this way, in a first embodiment, the present invention provides a method for the preparation of the tissue regeneration system like that of the present invention characterized because it contains the stages of:

a. isolation and purification of collagen from the small intestinal submucose;
b. design of collagen structures of determined thicknesses;
c. design of sterilized titanium meshes in diverse geometric shapes;
d. adhesion of the isolated and purified layers of collagen within the titanium meshes until the device is achieved.

In another preferred embodiment, the method of the present invention is characterized because the adhesion of the layers of collagen is performed by superposing multiple layers of collagen on the titanium meshes and later two to six additional layers of collagen are added on the titanium mesh.

In another embodiment, the method of the present invention is characterized because the superposition of the layers of collagen are performed without rotation in each additional layer.
In another embodiment, the method of the present invention is characterized because the superposition of the layers of collagen are performed with a 90° rotation in each layer that is added.

In another preferred embodiment, the method of the present invention is characterized because the stage of adhesion of collagen layers on the titanium mesh are done in a sterile area with lamina flow.

In another embodiment, the method of the present invention is characterized because after the superposition of the collagen layers and the titanium mesh, the resulting tissue regenerative device is left to dry for a period of 12 to 24 hours in a sterile area.

In another embodiment, the method like that of the present invention is characterized because after it is dried, the resulting product is cut and packaged.

In an embodiment, the method like that of the present invention is characterized because the resulting product is sterilized in ethylene oxide, gamma radiation, radiation with electrons or ultra-violet radiation.

Therefore, this invention is related to an implant graft adequate for various medical applications and its production process. Specifically, the small intestinal submucose of porcines is purified through an established process and is adhered to a titanium mesh with varied designs depending on the clinical use it will be given. This combination of two materials has not been described in international medical literature, nor have its clinical applications, given that for tissue regeneration, compounds do not exist with collagen and titanium that achieve the combination of the individual benefits of each material to strengthen their benefits.
The combination of two materials in this case with the small intestinal submucose that basically is composed of collagens and the Titanium frame has not been described nor therefore, classified, although it would be the union of a xenogeneic material (originating from another species) and an alloplastic material (graft made of plastic, metal or other material foreign to the human body), which would result in a Xeno-Alloplastic graft.

The necessary characteristics for the clinical applications of this compound are biocompatibility; biomechanical resistance to stress and compressive forces; the ability to be set by screws, tacks, staples or sutures; regenerative activity; resistance to infection, in addition to being able to be produced in different sizes and thicknesses, with different designs for the metallic frame that permits the material to be molded according to its use and afterward stability is shown throughout the healing period. The combination of the two materials also should be provided in a sterile manner for its clinical use.

RAW MATERIALS

A. INTESTINAL SUBMUCOSE

The porcine intestinal submucose is a natural derivate obtained from the pig's small intestine. It is found between the mucose layer and the muscular layer. It's constitution is mainly type I-III and VI collagen with a secondary contents of carbohydrates and lipids, it is totally a cellular, biocompatible, implantable in humans and reabsorbable.

The submucose induces the remodeling of the objective tissue, joining in, and resulting on functional tissues. In addition, this process includes a fast angiogenic response, a mononuclear cell infiltration during the post implant period, and the deposition of a new matrix to replace the SIS matrix.
Regarding the angiogenesis or vascular neoformation, is known to be needed for the supportive invading cells nutrition, same as for the elimination of discharging products from the cells. It allows the blood stream to irrigate, acting as a defense against infectious agents that could take over the support, and removes its demotion.

Four advantages of SIS collagen (SMALL INTESTINAL SUBMUCOSE) could be highlighted:
- Non-immunologic adverse response after implantation in xenogeneic guests.
- Ease of tissue remodelation.
- Allows specialized tissue differentiation and proliferation.
- Promotes infection resistance.

Advantages of the Porcine Intestinal Submucose

The advantages of these membranes are: it's excellent resistance for fixing and replacing the damaged tissues, ease to handle and high biocompatibility. In addition, it does not show the two big issues other grafts have. The SIS does not encapsulate nor dissolve. The encapsulation suffered by grafts is due to a response of strange body reaction, resulting in non-functional tissue and a rigid scar. On the other hand, its incorporation process produced by its components that are basically active proteins in charge of tissue regeneration, result in a more effective and faster healing process.

B. TITANIUM MESHES

Titanium is the ninth most abundant element and the fourth most abundant structural metal on the earth's crust. Large deposits of rutile and ilmenite ore are located in the United States, Canada and Australia. Titanium ore is treated with chlorine gas to produce an intermediate titanium chloride product.
The titanium chloride is reduced with either magnesium or sodium metal to titanium metal granules. The resultant granules are pressed into a dense compact, and the compacts are welded together to form an electrode for vacuum melting. An electric current is passed through the electrode for vacuum melting. An electric current is passed through the electrode in a vacuum arc furnace to produce a titanium ingot. The remelted ingot is further processed by conventional metalworking techniques to produce bars, wires, sheets, plates and tubular products.

**Composition**

Four grades of unalloyed titanium are known as commercially Pure (CP). Grades 1, 2, 3, or 4 are available with a stable alpha phase microstructure. The primary difference is related to oxygen content. The strength of unalloyed titanium increases as the oxygen content increases from grade 1 through grade 4. Small quantities of nitrogen and carbon tend to stabilize the alpha phase. The composition requirements of the four unalloyed titanium grades are precisely controlled and documented in ASTM F 67 specification for surgical implant material.

Composition limits are also specified in the ISO 5832-2 international standard.

**Properties**

Two important physical properties of titanium for implant applications are the density and modulus of elasticity. The density of unalloyed titanium is 56% the density of wrought 316 L satin steel and about 53% the density of cast Co-Cr-Mo alloy. The low density of titanium yield to a weight reduction of nearly 50% when implants of similar dimensions are compared. The weight reduction represents a patient comfort factor especially for large sized implants.
Elasticity modulus or Young's modulus, is a physical property of a material that describes the stress per unit strain in the elastic region. A material with high modulus of elasticity will transfer less stress from the implant to the bone.

The tensile properties of unalloyed titanium are dependent on grade and type or metallurgical processing. ASTM F 67 specification outlines the minimum mechanical properties that must be met in the annealed or softest condition. ISO 5832-2 international standard also covers annealed mechanical properties for grades 1, 2, 3, 4A, and includes Grade 4B in the cold work condition.

Moderately to highly stressed implants are normally fabricated from cold worked material. Titanium can be cold worked to produce high tensile properties that area nearly equivalent to cold worked 316L stainless steel. Unalloyed titanium is generally not capable of attaining extremely high tensile strength. Consequently, these small diameter implants are also available in Ti-6AL-4V alloy with a moderately high tensile strength of around 920 Mpa.

ASTM f 67 requirements (UTS), minimum 0.2% yield strength, and minimum elongation rate identical for bars, wires, sheets, strips and plates. Additional mechanical property requirements for unalloyed titanium sheet, strip, and plate include maximum 0.2% yield strength. Maximum yield strength and bend test requirements ensure that titanium flat mill products can be fabricated into various implant shapes in both the transverse and the longitudinal planes.

Fatigue

Fatigue is defined as the process of progressive, permanent structural change occurring in a material that is subjected to altering stresses and strains. The alternating stress and strain effects are usually localized and may produce cracks or complete fracture after sufficient number of cycles.
Unalloyed titanium fatigue life is influenced by many factors including composition, grain size, processing history, surface finish, residual surface stress and ultimate tensile strength. Major test dependent variables include type of alternating load, specimen geometry frequency, and test environment.

**Corrosion**

The superior corrosion resistance of unalloyed titanium and titanium alloys compared with nickel or iron based implants is well documented in literature.

Some of these publications conclude that titanium and some of its alloys may be the most biocompatible and corrosion resistance metallic implant materials in present use.

Titanium readily forms a passive surface film, which provides a high degree of immunity against attack by most mineral acids and chlorides. The ability of a passive film to repassivate readily if the film is scratched, abraded or disrupted is considered and important feature of any highly corrosion resistant material.

Low iron content in the unalloyed titanium microstructure has been shown to improve the stability in the protective oxide film.

The mixing of unalloyed titanium with implant quality 316L stainless steel should be avoided to eliminate any possibility of galvanic corrosion or accelerated fretting corrosion. Many of the advantages of unalloyed titanium such an improve corrosion resistance, improved biocompatibility, and absence of allergic reactions may not be realized with a mixed metal system.

**Biocompatibility**

As early as 1940, Bothe and colleagues concluded that unalloyed titanium pegs were well tolerated in animal model and the biocompatibility was similar to stainless steel or Co-Cr-Mo alloy. Leventhal with rabbits and rats and reported
in 1951 that titanium was inert and appeared to be ideal for fracture fixation. Brunski concluded that good tissue response was obtained when pure titanium dental implants were evaluated in beagle dogs.

Organ culture studies at the laboratory for experimental surgery have demonstrated the excellent growth development of embryonic rat femora implanted with titanium rods.

Dobbs and Scales, have reported that to their knowledge "there are not reports that suggest the metal sensitivity or adverse reactions of any kind are associated with titanium implants". That is in contrast to various clinical studies which have shown that metal sensitivity has been observed with implants in 316L stainless steel and Cr-Co-Mo alloys.

Unalloyed titanium also exhibits unique biocompatibility properties, which include soft tissue and bone adhesion to the titanium surface.

**Clinical Features of Titanium**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Clinical advantage</th>
</tr>
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<tbody>
<tr>
<td>Excellent corrosion resistance</td>
<td>Permanent implants</td>
</tr>
<tr>
<td>Excellent biocompatibility</td>
<td>Tissue attachment for better fixation</td>
</tr>
<tr>
<td>Non allergenic</td>
<td>Absence of metal sensitivity</td>
</tr>
<tr>
<td>Low density</td>
<td>Lightweight implants</td>
</tr>
<tr>
<td>Excellent ductility</td>
<td>Easily contoured</td>
</tr>
<tr>
<td>Four grades</td>
<td>Implant design versatility</td>
</tr>
</tbody>
</table>

*Sterilization*: implants may be sterilized by any of the standard methods such as steam autoclave, ETO, gamma radiation and RF discharge.

*Implant handling*: Excessive finger print contamination from handling, may produce slight discoloration after repeated steam autoclave cycles. No adverse effects are related to this change in surface appearance.
**Diagnostic imaging:** X-radiography, magnetic resonance imaging and CT scans, and PET scans can be utilized. MRI scan resolution is superior to 316L stainless steel because titanium produces less starburst or signal interference.

**Implants retrieval:** occasional back deposits (wear debris) may be observed at implant removal sites. No adverse tissue reaction is associated with this clinical observation.

The alloplastic component of this Titanium-collagen compound is made with unalloyed titanium. Thickness of this frame can vary between 0.1mm to 1.5 mm, they are designed to facilitate contouring and fixation with Standard 1.0mm. up to 2:30 mm., Titanium screws; different titanium chemical surface treatments can be used to increase the thickness of the naturally occurred titanium oxide film. Titanium surface can be rough or highly polished depending on the proposed clinical use for this Titanium-collagen compound.

**Size:** It can be produced from small sizes 1 X 1 cm., up to the largest size of 25X25 cm.

Regarding to the procedure disclosed in the present invention, it essentially consists of:

- Production of small intestinal (porcine) submucose membranes, based on a new methodology for the isolation and purification of the collagen.

- Design of different titanium meshes.

- Adhesion of the two previously mentioned materials for the formation of a new compound.

- Description of the procedure for the adequate use of membranes with titanium in different reconstructive medical situations.
DETAILED DESCRIPTION OF THE INVENTION

The process of this invention involves specifically the following stages:

Obtention of the small intestine

The intestine of porcines is obtained in accordance with the necessary requirements with regard to their raising, upbringing and upkeep to comply with the demands for them to be competent for this process to be performed. Attending the sacrifice of the animals and dissecting the abdomen, the yeyunum is then identified and approximately 1.5 to 2.5 meters of this is obtained. The intestine is then placed in a freezer for transport.

Incorporation of the Titanium Frame, Dehydration and Cut

The procedure that follows takes place in the sterile nucleus under extreme asepsis and sterile conditions.

In the sterile area under the lamila flow, the membranes are stretched over sterile plastic on flat surfaces.

The sterilized titanium meshes of different sizes and designs are prepared that have been previously produced under the aforementioned international standards with different surface treatments in accordance with the use they will be given (Meshes with orifices of 1.0, 1.5, 2.0 and 2.3 mm., H, Y, half-moon shapes, etc.).

From two to up to six layers of purified submucose are superposed rotating the longitudinal axis every time that a new 90-degree layer is superposed. The titanium mesh is placed in such a way that the hydrated submucose remains completely covered on one of its sides, it doesn’t matter which. Then new layers
are added over the side of the titanium mesh that has remained uncovered, from one and up to six layers exactly as the first side was performed, making a 90-degree rotation each time a new layer is added.

Much care should be taken so that air bubbles don't remain trapped between each one of the purified submucose layers, which can impede the perfect embedding of the material. Once this process is completed, the collagen and titanium compound remains exposed to the lamina flow for a period of 12 to 24 hours, until the collagen dehydrates and all the superposed layers are incorporated within it leaving the titanium mesh trapped within the collagen.

Packaging

The membranes obtained in this manner are packaged, and cut within the sterile nucleus using guillotines and scissors for metal. They are transferred to the sterilization center with ethylene oxide.

a. GENERAL FUNCTIONS OF THE TITANIUM-COLLAGEN COMPOUND

i. Container:
The function of the container of filler materials with its origin not being of importance, is given by the collagen membrane, which due to its mechanical characteristics is capable of supporting tensions and pressures and of adapting to the relief given by the filler used. At the same time, it permits the passage in both directions of small molecules as nutrients that help maintain the viability of autologous grafts.

ii. Barrier:
the materials such as the collagen that function as a selective barrier impede the passage of cells through their pores to impede the mixing of tissues and organize the regeneration process. The size of the pore of the collagen of the small intestinal submucose oscillates between 10 and 100
microns acting as a selective barrier that permits the passage only of nutrients through its pores.

iii. **Tri-dimensional Outlines:**

the ductility of the titanium mesh makes it easily malleable to be molded in a tri-dimensional shape permitting the stability of the shapes. The elasticity module of the collagen permits the compound to be deformed and manipulated in accordance with its needs. The design of the meshes with orifices makes the material capable of being set with the use of screws to healthy osseous surfaces neighboring the defective area.

iv. **Absorption of Pressure and Tensions:**

A material with a high module of elasticity will transfer less implant forces to the bone. Therefore, the mix of these two titanium and collagen materials will make the absorption of forces responsible for the reabsorption and deformation of grafts possible.

v. **Tissular Regeneration:**

The excellent biocompatibility of both materials added to the chemical composition of the submucose, composed of an important group of proteins known for their tissue-regenerating role, make the compound act within the regeneration of the committed tissues in each one of the procedures in which it will be used.

B. **Instructions for the use of the small intestinal submucose membranes with a titanium frame in reconstructive surgery:**

The systemic evaluation of the patient is always necessary, which determines that the condition of the patient is apt for the implantation of the membrane(s). The use of membranes in patients with uncontrolled systemic diseases such as
diabetes, lupus, a history of allergic reactions to porcine or collagen derivatives; in infected wounds or with any sign of infection is contraindicated.

i. maxillofacial trauma

• Bony regeneration of alveolar edentulous where in vertical and/or cross-sectional sense is required to increase the lost bone.
• In partial defects or total reconstructions of maxillary defects through the use of particularized or block bone grafts.
• Bony regeneration of defects in the skull-facial area that requires handling of contour in areas under pressures or tension (Floor or other walls of the orbit, walls of the maxillary sinus, reconstruction of bony defects in contour of the jaw).
• Regeneration of periodontal defects of various walls.
• Small periodontal defects around teeth or implants where vertical regeneration is required.

ii. Otolaryngology

• Surgical reconstruction of sinus walls.
• Nasal septum perforations.

iii. General Surgery

• Surgical reinforcement of abdominal wall in eventrations and hernias.

iv. Neurosurgery

• Spinal discs replacements.
• Reconstruction of skull bony defects.

v. Orthopedics

• Surgical reconstruction of bone long defects.
c. Evaluation of membranes

A series of in Vitro and in vivo tests have been performed to evaluate SIS collagen membranes.


A Stress Strain Test was performed under the ASTM 882 norm (standard stress strain test for polymeric films) where the maximum loading, deformation and ultimate strength were measured. The effect of the number of layers (simple (1), overlapping simple (1o), two (2) and four (4) layers) and of the orientation (longitudinal (L) and transversal (T) to the intestinal axis) were researched. A factorial experimental design was used with two factors, four levels in the number of layers and two in the charge direction, with n=5 replicas. A statistical analysis was performed using the Tukey Test.

The maximum load appeared to be affected by the number of layers, with it being significantly higher in the 4L group, when comparing it with the 1L, 1oL and 2L groups; and in the 4T group, when comparing it with the 1T and 2T groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>Maximum Load</th>
</tr>
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<tbody>
<tr>
<td>1L</td>
<td>8.4 ± 0.5 N</td>
</tr>
<tr>
<td>1oL</td>
<td>13.3 ± 7.0 N</td>
</tr>
<tr>
<td>2L</td>
<td>10.5 ± 3.9 N</td>
</tr>
<tr>
<td>2T</td>
<td>13.1 ± 5.9 N</td>
</tr>
<tr>
<td>4L</td>
<td>22.1 ± 9.7 N</td>
</tr>
<tr>
<td>4T</td>
<td>13.1 ± 5.9 N</td>
</tr>
</tbody>
</table>

The maximum load was higher for all the configurations that were oriented longitudinally in comparison to the ones oriented transversally, with a significant difference for the 2 and 4 layers. On the other hand, no significant difference of
the maximum deformation was seen with different number of layers nor with a change of direction. Nor was a significant difference of maximum strength found, since a larger number of layers increase the maximum load as much as the transversal area. The stress resistance does not differentiate between the number of layers which proves that the union is good and reliable. It was concluded that the maximum load allowed can be increased with a significant difference creating configurations of 4 layers of membranes oriented longitudinally. This makes these configurations adequate to treat lesions exposed to high loads, such as inguinal hernias. The direction of the highest load applied to the lesion should also be analyzed with the medical specialist with the aim of orienting the membrane longitudinally in that direction. Taking into consideration that the mechanical properties of the configuration of an overlapping simple layer are similar to the ones of a simple layer, it would also be possible to use configurations of overlapping layers for use in large-area lesions.

e. Experiment: Culture of Cells in the Membrane

A planting of fibroblasts and keratinocytes on SIS membrane supports were conducted. They were incubated for four weeks at 37°C and 5% CO2. A stress strain test was conducted in which a resistance to stress between 3.5 and 19.45 MPa were obtained, and the viscous-elastic behavior of the material was evidenced. The values found for the sown supports were greater than those found for the control models (exposed to a cell-free medium in the same conditions as the sown supports).

High adhesion, growth and proliferation of cells distributed throughout the support and metabolic activity were found given the production of the extracellular matrix. The results of this study allowed an adequate biological response to the supports to be predicted with the objective of implants in humans for the production of connective tissue and artificial epithelial tissue.
f. CLINICAL RESEARCH: Maxillofacial Results

Guided tissue regeneration was performed on 46 healthy volunteer patients that required the handling of maxillary defects with autologous bone grafts, using the collagen membranes according to the protocol described in this document for the use of the membrane in maxillofacial surgery. The systemic and local response was measured after the implantation of the membranes. The postoperative results were clinically and radiographically valued. The clinical biocompatibility analysis included the measurement of pyrogenicity, systemic toxicity and allergies.

The group was comprised of 29 women and 16 men ranging in age from 21 to 76 years with an average age of 48.5 years. The bone defects were classified into four different groups: trauma defects (6), by infection (8), by atrophy (31) and by mechanical apparatus (1).

Panoramic and periapical radiographies of the defects in the preoperative, in the immediate postoperative period and three and six months later were taken of each of the patients. The evaluation of the radiographic changes were conducted in accordance with the surgeon's criterion. The patients were evaluated to measure acute systemic toxicity observing any related sign or symptom such as general discomfort, diarrhea and vomiting. The pyrogenicity of the material was evaluated taking body temperature readings using a standardized monitor for vital signs. Body temperature readings were taken immediately before the surgery and on the fifth postoperative day. The allergic response to the material was evaluated analyzing in situ changes and searching for any type of changes at the systemic level such as pruritus, urticaria and skin eczema, etc., that would suggest a clinical chart of allergic reactions.

Patients belonging to all the groups showed that there were no adverse reaction after the implantation of the material. The postoperative of the totality of the sample occurred under normal conditions. No patient showed symptomatology
associated to acute intoxication, allergic reactions or fever. The average body temperature of the patients in the immediate postoperative was 37.04°C and on the fifth postoperative day it was 37.05°C, which is not significantly different for the evaluation of pyrogenicity.

42 patients had satisfactory radiographical and clinical results. Four complications in patients were observed who had had dental implants associated with their healing process in the late postoperative. All the patients who showed complications belonged to the atrophy defects group.

g. Study: Evaluation in Cutaneous Ulcers

The collagen membranes were implanted in 30 patients with cutaneous ulcers following the protocol described in this document for the use of the membranes in plastic and reconstructive surgery. Complete closure of all the wounds was obtained.

Therefore, the focus of the present invention in the next main aspects:

a. A methodology for the isolation and purification of the collagen.
b. A methodology for purified small intestinal submucose collagen adhesion onto a titanium structure.
c. Design of several different collagen structures in many thickness that varies it's biomechanical features, making it possible for the device to have clinical versatility.
d. Collagen-Titanium compound variations based on thickness and proportional changes of both collagen and titanium materials.
e. Clinical applications for the use of the collagen membranes reinforced with a titanium frame

Other characteristics and aspects of this invention will be valued and found by those experts in the field, once they read and understand the specification
content. Such characteristics, aspects and variations and modifications are clearly contained within the reach of this invention.

OBJECTIVES AND ADVANTAGES OF THE INVENTION

• The present invention provides a new alternative for tissue remodeling and reconstruction, using intestinal submucose membranes that contain a titanium mesh which will make them capable of supporting compression and tension loads, imitating tri-dimensional geometric shapes.

• This device makes possible for this material (collagens) to maintain its demonstrated biological qualities, such as its excellent regenerative capacity.

• The device of the present invention intended for guided tissue regeneration is applicable in several fields of reconstructive surgery, where this characteristic provided by the Titanium frame is required, in order to be molded, to support loads and to be set.

• The innovative device of the present invention will function as a container capable of maintaining the tri-dimensional shape that it's molded into, and as a barrier to impede the penetration of cells that are different than those that are grafted within the matrix.

• The uses of the present invention would be in medical specializations such as oral and maxillofacial surgery, plastic and reconstructive surgery, orthopedics, general surgery, back surgery and neurosurgery.

• The use of these membranes will be an option within the area of general reconstructive surgery as a co-adjuvant of the regenerative processes, to achieve an effective organization of this event and the creation of tissues, such as bone, from which a desired geometrical shape will be obtained.

• The preparation method for this invention for tissues regeneration is simple.
CLAIMS

It is claimed that:

1. A device for tissue regeneration characterized because it contains collagen membranes originating from the intestinal submucose and a titanium mesh of diverse geometric configurations, in such a way as it is integrated into a titanium-collagen structure.

2. A device for tissue regeneration according to claim 1, characterized because of the collagen originating from the intestinal submucose is of a warm-blooded vertebrae.

3. A device for tissue regeneration according to claims 1 to 2, characterized because the collagen originating from the intestinal submucose is from a porcine.

4. A device for tissue regeneration according to claims 1 to 3, characterized because the titanium-collagen device has a thickness that varies between 0.1 and 1.5 mm and a size that varies from 1x1 cm to 25x25 cm.

5. A device for tissue regeneration according to claim 4, characterized because the device has a thickness that varies between 0.3 and 1.2 mm and a size that varies from 5x5 cm to 20x20 cm.

6. A device for tissue regeneration according to claim 5, characterized because the titanium-collagen device has a thickness that varies between 0.5 and 1.0 mm and a size that varies from 10x10 cm to 15x15 cm.
7. A device for tissue regeneration according to claims 1 to 6, characterized because the titanium mesh is flat with the capacity to be molded.

8. A device for tissue regeneration according to claims 1 to 7, characterized because the titanium mesh has 3-D shapes.

9. A device for tissue regeneration according to claims 1 to 8, characterized because the titanium mesh has Y, H, half-moon, quadrangular, rectangular shapes.

10. A device for tissue regeneration according to claims 1 to 9, characterized because the titanium mesh has orifices from 1.0 to 2.3 mm.

11. A device for tissue regeneration according to claims 1 to 10, characterized because the titanium mesh has orifices of 1.0 mm.

12. A device for tissue regeneration according to claims 1 to 10, characterized because the titanium mesh has orifices of 1.5 mm.

13. A device for tissue regeneration according claims 1 to 10, characterized because the titanium mesh has orifices of 2.0 mm.

14. A device for tissue regeneration according to claims 1 to 10, characterized because the titanium mesh has orifices of 2.3 mm.

15. A device for tissue regeneration according to claims 1 to 14, characterized because it incorporates from one layer of collagen to multiple layers of collagen.
16. A device for tissue regeneration according to claim 15, characterized because it incorporates from one layer of collagen to six layers of collagen.

17. A device for tissue regeneration according to claim 16, characterized because it incorporates from two layers of collagen to four layers of collagen.

18. A method for the preparation of the tissue regeneration device according to claims 1 to 17, characterized because it contains the steps of:

   a. isolation and purification of collagen from the small intestinal submucose;
   b. design of collagen structures of determinat thicknesses;
   c. design of sterilized meshes of titanium in diverse geometric shapes;
   d. adhesion of the isolated and purified layers of collagen within the titanium meshes until the device is achieved.

19. The method according to claim 18, characterized because the adhesion of the layers of collagen is done by superposing from two layers to multiple layers of collagen on the titanium mesh and later adding from two to multiple layers of collagen on the titanium mesh.

20. The method according to claim 19, characterized because the adhesion of the layers of collagen is done by superposing from two layers to six layers of collagen on the titanium mesh and later adding from two to six layers of collagen on the titanium mesh.

21. The method according to claims 20, characterized because the adhesion of the layers of collagen is done by superposing from two layers to six
layers of collagen on the titanium mesh and later adding from two to six layers of collagen on the titanium mesh.

22. The method according to claims 18 to 21, characterized because the superposition of the layers of collagen are performed without any rotation in the addition of each layer.

23. The method according to claims 18 to 22, characterized because the superposition of the layers of collagen are performed with a rotation of 90° in the addition of each layer.

24. The method according to claims 18 to 23, characterized because the adhesion phase of collagen layers on the titanium mesh are done in a sterile area with lamina flow.

25. The method according to claims 18 to 24, characterized because after the superposition of the collagen layers and the titanium mesh, the resulting tissular regenerative device is left to dry for a period of 12 to 24 hours in a sterile area.

26. The method according to claims 18 to 25, characterized because after it is dried, the resulting product is cut and packaged.

27. The method according to claims 18 to 26, characterized because the resulting product is sterilized in ethylene oxide, gamma radiation, radiation with electrons or ultra-violet radiation.
FIGURE 1

Túnica serosa
Túnica muscular
Túnica submucosa
Túnica mucosa