(MAA)DE-4-U Mesh: A Novel Polypropylene Hernia Mesh Coated with a Methacrylic Acid Copolymer Coating

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Clinical Need:

Hernias occur when an internal organ or internal body part protrudes through the muscle or tissue wall, most often causing a bulge or swelling. Hernias are caused by muscle weakness in the abdominal wall and may result from high strain activities [1]. Approximately 20 million hernias are repaired around the world every year [2]. The most common type of hernia is an inguinal hernia, where the fatty tissue of the intestine protrudes through and into the groin and inner thigh area. Inguinal hernias account for approximately 70-75% of all hernia occurrences [2]. Other hernias include femoral hernias, occurring at the top of the inner thigh, umbilical hernias, located near the navel, and hiatal hernias, where the stomach pushes up into the chest cavity through the diaphragm. Some uncommon hernia types include incisional, epigastric, spigelian, and diaphragmatic hernias [3].

Over one million hernias are treated in the United States alone every year [4]. The most common treatment for hernias includes a mesh implantation surgical procedure. Hernia meshes are widely accepted as the optimal hernia repair method, over surgical suture techniques. In fact, more than 80% of hernia repairs in the United States utilize mesh products [5]. Surgical meshes are successful because they are able to securely reinforce and strengthen the weakened abdominal area. They also aim to promote tissue regeneration into the affected site to aid in healing and long term stability [6].

Although hernia meshes are the most widely accepted hernia repair method, they remain imperfect. The most common mesh material is non-resorbable polypropylene (PP), which is necessary to retain strength and stiffness in the abdominal area, but can cause a chronic inflammatory response at the wound site and can ultimately lead to adhesions and mesh migration. Various methods have been devised to reduce this inflammatory response resulting from these PP meshes, with the most common being the reduction of the polymeric density of polypropylene. Low-density polypropylene provides two times the force resistance to the abdominal wall and is more flexible to improve abdominal wall integration but induces a less intense chronic inflammatory response to improve wound healing [7]. Lighter PP allows for firm integration into the surrounding abdominal wall while decreasing the degree of adhesion [7].

There are currently over 70 different surgical meshes available to aid in hernia repair [6]. The ideal surgical mesh has yet to be found because all approved meshes have shown some post-surgical concerns for patients. Lightweight PP has been one scientific discovery on the journey to finding the “ideal” hernia mesh, but even with this density reduction, complications still occur. Post-surgical complications for a hernia mesh implanted patient can include chronic

pain, infection, recurrence, adhesion, and bowel obstruction [8]. These complications mainly stem from the development of mesh shrinkage, intense inflammatory response, acute foreign body reaction, and mesh movement post-implantation [9].

As a result, there is a need for a hernia surgical mesh that results in less post-implantation complications for the patients. The less complications experienced by patients, the less likely hernia recurrence is. The national range of cost per hernia mesh repair procedure is $3,900-$12,500, which equates to about 125 trillion dollars per year [10]. Creating a more advantageous hernia mesh would not only save patients from physical discomfort, but would also ideally save them time and money from having to go through hernia revision surgery.

Innovation:

In order to address some of the current complications associated with hernia mesh implantation, we propose the addition of a non-bioresorbable methacrylic acid (MAA)-copolymer coating to a lightweight polypropylene surgical mesh. MAA-based materials are known to be vascularly regenerative materials that aid in the acceleration of wound healing and do not initiate a strong foreign body response [11,12]. To make MAA into a thermoplastic coating and to avoid it's water soluble characteristics, it can be copolymerized with hydrophobic isodecyl acrylate (IDA) [13]. Based on preliminary data gathered and summarized in the article "Methacrylic Acid Copolymer Coating Enhances Constructive Remodeling of Polypropylene Mesh by Increasing the Vascular Response", the addition of Poly(methacrylic acid-*co*-isodecyl acrylate) with 40% MAA (MAA-*co*-IDA, 40% MAA) to PP mesh resulted in a tissue response that was biased toward vascularization instead of fibrosis, a dampened foreign body response and lessened inflammation [14].

(MAA)DE-4-U Mesh

Device Features and Specifications

Our mesh will be designed similar to current PP hernia mesh models already being implanted, such as Prolene by Ethicon or BARD® 3DMAX™ Light Mesh. We will create a macroporous, lightweight PP mesh by warp knitting monofilament light PP together. Once the PP mesh has been created, then the MAA-copolymer coating can be added. We will be following the same coating process as practiced in the article entitled "Methacrylic Acid Copolymer Coating Enhances Constructive Remodeling of Polypropylene Mesh by Increasing the Vascular Response" [14]. PP meshes can be hard to coat due to their lack of polar groups and low surface energy . To enhance the surface energy, the PP mesh will be pretreated using glow discharge plasma and acid etching [14].

After pretreatment, the mesh will be spray coated with the MAA-*co*-IDA, 40% MAA coating. The percent MAA used in the coating can affect the efficacy of vessel formation and

how the body reacts to the mesh. It has been shown that 40% MAA creates sufficient vessel formation, whereas 20% does not [14]. The coating will be applied three times to ensure full mesh coverage. Each layer of coating will add about .15mg of polymer to the mesh. The coating will run along the PP filaments and will not have a drastic impact on the pore size of the mesh [14].

Preliminary Data

The preliminary data collected and provided in "Methacrylic Acid Copolymer Coating Enhances Constructive Remodeling of Polypropylene Mesh by Increasing the Vascular Response" supports that the mesh coating results in a less aggressive foreign body response. It was shown that coating the mesh results in more vascularization and less fibrosis, and that the coating does not interfere with tissue integration into the mesh. Certain test methods were performed to determine pretreatment's impact on the coating integrity, and then testing was done to analyze the differences between uncoated and coated meshes in vivo. The data that was collected can be found in the original article [14]. MAA was chosen as the coating material due to other research that showed its mechanism of action. Macrophages that come in contact with MAA secrete more insulin growth factor 1, increasing endothelial cell proliferation and migration resulting in higher vessel densities in the surrounding tissue. It was also shown that the increased vascularization improved healing, and that there was no pronounced foreign body response in reaction to the MAA [15].

The mesh is pretreated to allow for better coating adhesion. It was found through x-ray photoelectron spectrometry that the pretreatment increased the quantity of oxygen on the surface of the mesh, meaning more hydroxyl, carbonyl, and carboxylic groups were available for bonding. This was further shown through contact angle measurements, as the contact angle was lower on pretreated samples. This means that the mesh became more hydrophilic and had a higher surface energy after the pretreatment was applied. SEM imaging showed that on pretreated mesh, the coating followed the fibers more closely and did not cover the pores of the mesh, likely meaning it would impact tissue integration less than mesh that was not pretreated. DAPI staining showed that MAA fully coated the mesh, as the MAA became visible under fluorescent microscopy. After being incubated at 37 C for three weeks, the samples that were not pretreated showed that the coating had completely peeled away. No MAA was detected under fluorescent imaging after DAPI staining, and the fiber striations observed under SEM imaging looked similar to how the uncoated samples looked. The pretreated samples appeared to have swelled, because the fiber striations could no longer be seen - but the coating was still present, adhered, and even. Overall, the results showed that the pretreatment was essential for the coating to properly adhere to the mesh.

The meshes were implanted in a subcutaneous model in mice just above the dorsal muscle. After one to three weeks, the implant was removed and analyzed through

immunohistochemistry and qPCR. Vessels and cells in the surrounding connective tissue within 100 micrometers of the implant were counted, and the local cellularity index was counted - which is the ratio of the area adjacent to mesh fibers that is occupied by cells to the total area of the mesh fibers. The meshes analyzed at one week showed that the tissue was successfully growing into the pores of the mesh in both the coated and uncoated samples. This showed that the coating did not negatively affect integration. At two weeks, the samples were stained using Masson's Trichrome stain for alpha-smooth muscle actin and endothelial cells (CD31) to visualize the forming vessels. The vessel density surrounding the coated mesh was double that of the uncoated mesh. It was clear that the MAA was in fact promoting vascularization as intended. This cellularity hit its maximum at one week and decreased in succeeding weeks for both groups. Each week the cells were found to be distributed evenly around the coated mesh, but they were concentrated on the fibers in the uncoated mesh. Therefore, the cellularity of the coated mesh was consistently lower than that of the uncoated mesh, though significantly so at weeks two and three. When viewing the immunohistochemistry under high magnification, it was clear that the uncoated mesh had attracted and resulted in several multinucleated foreign body giant cells (FBGCs) and that CD68 positive macrophages were also present. CD68 is used as a histochemical that indicates inflammation [16]. The coated mesh sample had half the amount of CD68 positive macrophages, had fewer macrophage makers and proinflammatory cytokines expressed (Tgf-β1, Tnf-α, and Il1-βTgf-β1, Tnf-α, and Il1-β). A similar expression of anti-inflammatory cytokines (Il10, Il6) was found. It was also observed through picrosirius staining that the collagen surrounding the coated mesh was less dense and aligned than that surrounding the uncoated mesh. These results show that there was a stronger foreign body response to the uncoated mesh, while the coated mesh did not result in an aggressive foreign body response.

Verification/Validation Testing

Overall, the preliminary data successfully shows that the MAA coating presented the intended impact of reducing the body's foreign body response to the mesh implant, without interfering with tissue integration. It helps promote vascularization instead of fibrosis, and at three weeks showed to result in fewer infiltrating cells, macrophages, FBGCs, proinflammatory signals and fibrogenic signals - leading to increased healing. The following experiments are proposed to verify that the MAA coating is safe to use and performs as described.

As for benchtop models, the intention is to show that MAA is not cytotoxic and that the coating does not impact the mechanical properties of the mesh. To show that MAA is not cytotoxic to cells, a direct contact method following ASTM F813-07 will be performed [17]. Five meshes without the MAA coating will be used as the control group, and each experimental group will also have a sample size of five. The samples in each experimental group will be pretreated prior to coating, and the experimental groups will include a (MAA-*co*-IDA, 40%

MAA) and (MAA-*co*-IDA, 80% MAA) coating, with sample representing pre- and post-sterilization. The meshes will be sterilized using ethylene oxide sterilization. An uncoated sterilized sample will be included in the experimental group to help determine the reasoning for potential differences in results. The 80% MAA sample is intended to show that even with an increased amount of MAA, the material is still not cytotoxic. The post- sterilization samples are to show that even with exposure to high heat and sterilizing chemicals, the material is not altered in a way that makes it cytotoxic. The cells used will be human skeletal muscle cells, and at days 1, 5, 7, and 14, the sample will be removed and cells outside the border of where the sample was previously placed will be imaged under a microscope for analysis. This is because it is likely that the cells directly under the sample may have been affected by its mechanical burden rather than its cytotoxicity. The passing criteria is that there is no significant difference between the cell count of any of the test samples. This will be determined using ANOVA statistic analysis. The other benchtop model will involve the use of an instron to test the mechanical properties of the coated and uncoated meshes. The tensile strength and modulus of the mesh in its hydrated state will be obtained. Fifteen uncoated and fifteen coated meshes will be prepared for this testing. The meshes will be immersed in phosphate buffered saline for twenty-four hours at 37C to fully hydrate the sample at body temperature. Since a modulus test is non-destructive, each sample will first be tested for its modulus and then immediately tested for its tensile strength. Only once one sample has been tested, should the next be removed from the incubator. The tensile strength is how much force the material can withstand prior to tearing. In order for the mesh to withstand in-vivo forces it may encounter, the mesh will need to test at least 32 N/cm in the strongest direction, and at least 16 N/cm in the weakest [18]. The modulus is a mechanical property that indicates the integrity of the material, calculated by applying a strain, measuring the stress caused, and taking the dimensions of the sample into consideration. Differing moduli between an implant and the surrounding tissue can cause a more aggressive foreign body response [19]. The passing criteria will be that the tensile strength of the mesh will be at least 32 N/cm in one direction, and at least 16 N/cm in the other of uncoated and coated samples, and that the modulus is not significantly different between the sample groups.

As for in vivo testing, the sterilized mesh will be implanted in a porcine model in the location of interest. A surgeon will replicate the surgery described in the Existing Procedure section included later in this paper, as closely as possible. The purpose behind this in vivo experiment is to verify that the coating lessens the foreign body response. A porcine model was selected due to its similarity in anatomy and its immune system when compared to that of humans [20]. Potential complications with using this model is that since a pig is a four legged animal, there will be increased pressure on the abdominal wall and implant. For this reason, testing in a porcine model is likely to be “worst case”. This study will involve sixteen animals and will last three years. Throughout the study, the animals will be observed for any change in behavior and food intake that might indicate pain or suffering. In these cases, the animal will be euthanized and the mesh will be explanted for analysis. Two animals with a coated mesh and two

with an uncoated mesh will be taken at one week, one month, six months, and years 1, 1.5, 2, 2.5, and 3 for analysis. During all explantations, the mesh should be observed for adhesions to the intestine, as these adhesions should not occur. Immunohistochemistry and imaging will be performed to observe the presence of any FBGCs and CD68 positive macrophages, just as was done when collecting the preliminary data. Additionally, the macrophage makers and proinflammatory cytokines should be screened for using qPCR. The passing criteria for this experiment is that the results show significantly less FDGCs, CD68 positive macrophages, macrophage markers, and proinflammatory cytokines expressed in the animals that have a coated implant. Additionally, eight more animals can be added to this experiment that are implanted with a competitor's mesh product. This would help prove that (MAA)DE-4-U Mesh is as effective as, if not more effective than, the competitor mesh.

Clinical Study Strategy

A clinical study will be organized in order to ensure the safety of patients implanted with (MAA)DE-4-U Mesh, and prove that it is effective. Patients will be selected for a clinical study based on their need for a mesh implant and their preexisting conditions. Patients with minimal preexisting conditions are preferred, so potential complications can be more directly identified and associated with the implant or procedure. Patients should not have undergone abdominal surgery within the past year to reduce happening upon complications regarding incomplete healing from a previous procedure. A handful of patients with diabetic issues may be selected to provide a sample showing that (MAA)DE-4-U Mesh is also a more safe and effective option for them. This is possible due to the mechanism of action of MAA discussed in the Preliminary Data section of this paper. The clinical study will be performed at multiple centers due to the familiarity of the specific procedure and to gather the most unbiased data possible. One surgeon does not need to perform every implantation, as the only difference is the coating on the item being implanted. Each implantation should be observed; however. It is important to take note of any complications that occur, observations that are made, or different techniques used during implantation, so that information can be referenced later if needed.

Regulatory Strategy

Although MAA coatings have been approved by the FDA for food contacting surfaces, there has not been an FDA approved implantable medical device that utilizes these coatings. Specifically, the mixture of MAA-*co*-IDA, 40% MAA has not previously been used as a coating for an FDA approved implantable medical device. Even Though MAA coatings may be a more recent discovery in regards to implantable devices, there has been a lot of promising preliminary research surrounding MAA copolymer coatings for medical devices over the past few years. For example, research showing how MAA beads produce a dampened foreign body response [12]. The macrophages that respond to implanted devices with MAA coatings are biased toward the

anti-inflammatory phenotype (M2) and additionally increase secretion of insulin growth factor 1. The secretion of IGF-1 enhances endothelial cell proliferation and migration and helps to improve healing of the affected site [14]

Based on the many PP hernia meshes already approved for surgical use, mixed with the uncertainty regarding MAA coatings on implantable devices, the (MAA)DE-4-U Mesh would be classified as a class II medical device and would need to be submitted to the FDA for a 510K approval. The (MAA)DE-4-U Mesh shares design principles with various predicate 510K devices that have been cleared for marketing in the United States, such as the HydroCoat Mesh, PROLENE Polypropylene Mesh by Johnson & Johnson and many more. If the (MAA)DE-4-U Mesh is proven to be as effective or more effective than the predicate devices, then it would gain justified use for an implantable hernia mesh and the company would move forward onto a commercialization plan for the device.

Market, Customer and Competition Analysis

Existing Procedure:

Inguinal hernias are the result of strain to the inner groin. Ultrasound imaging is used in some cases in order to identify the hernia. Magnetic resonance has been used to differentiate between inguinal and femoral hernias when a high sensitivity was used in order for a more precise diagnosis. Once a severe hernia has been identified, surgery is necessary. Smaller, less problematic hernias may repair themselves over time while the patient is monitored. For hernias that require surgery, a prosthetic material is used. Mesh is often chosen as this material and the specific mesh can be decided by the surgeon. Open and laparoscopic repairs are possible, but 90% are performed openly. After the surgery is performed, general wound care takes place over the next two to four weeks [21].

During open surgeries, the patient is put to sleep under general anesthesia, and incisions are made so that the herniated tissue may be pushed back or removed. The incision is closed with stitches and hernia mesh can be used if the area is large enough to warrant it [22]. During laparoscopic surgeries, a few small cuts are made in order to gain access to the area instead of a large one. Anesthesia is used, and the abdomen is inflated in with gas in order to get better access to the site. A camera is inserted into one of the incisions and mesh is guided to the area in order to patch it. Stitches or staples may be used to hold the mesh in place [22].

In a study of inguinal hernia repairs, 25 individual studies were examined which included 6293 participants. The study found that mesh repair reduced the risk of hernia complications when compared to non-mesh repair. Non-mesh repairs also had higher rates of neurovascular and visceral injuries. Mesh groups had a slightly higher risk of infection, and risk of seromas [23].

Using surgical mesh in hernia repair has become the standard of care for many. The most commonly used meshes are constructed of synthetic material or animal tissue. Those made of synthetic material are designed to be specifically abrsorbable or non-absorbable, or a

combination of both, depending on the intended surgical use. Non-absorbable mesh remains in the body permanently and reinforces the hernia. Absorbable mesh degrades in the body over time as new tissue grows. Animal-derived meshed can be made of processed, disinfected tissue, usually from a porcine or bovine source [24]. There are many negative impacts from hernia repairs, such as pain, infection, hernia recurrence, adhesion, seroma, and bowel obstruction. Once a surgical mesh has enough proof of complications, it is recalled from the market [24].

Synthetic meshes have many qualities that determine their success and biocompatibility such as filament type, tensile strength, elasticity and porosity. The weight and biocompatibility are also factors when deciding between meshes. Surgeons consider the use of a mesh before deciding which one to use. Most situations require only a light weight mesh, some made of polypropylene such as Parietene Light, Optilene, and Mersilene which have a lower risk of infection. Absorbable meshes such as Vicryl (polyglactin) or Dexon (polyglycolic) are used in infected wounds. Other meshes include Goretex (ePTFE), and Ethicon (polyester) [25].

Since our proposed technology is a polypropylene mesh coating, the procedure regarding synthetic polypropylene mesh deserves special focus. Polypropylene has favorable properties for hernia repair because it is chemically inactive, durable, and has high tensile strength [26]. A variety of polypropylene meshes and mesh-like products have been created over time.

Competition:

Since hernias are a common occurance and the clinical need for repair is high. There are a number of manufacturers who produce hernia mesh products [27].

MANUFACTURER	HERNIA MESH PRODUCT LINES
Atrium	C-QUR, Vitamesh, Proloop, Prolite, Prolite UltraQ
Bard	3DMax, AlloMaxBard Soft Mesh, Bard Mesh Sheets, Composix, Dulex, Kugel, MK Patch, OnFlex, PerFix Plug, Phasix Mesh, Phasix, Sepramesh IP Composite, Ventralex, Ventralight, Ventrio, Visilex, XenMatrix Surgical Graft
B. Braun	Premilene, Omyra, Optilene
Ethicon	FlexHD Structural, Physiomesh, Proceed, Prolene, Ultrapure, Ultrapure Advanced, Vicky, XCM Biologic
Gore Medical	Bio-A, Dual mesh, Micromesh, Gore-Tex Soft Tissue Patch, Sinecure
LifeCell Corporation	Alloderm Select, Strattice
Medtronic	Parietex, Permacol, ProGrip, Symbotex, Versatex
TELA Bio	OviTex

Atrium's meshes and mesh plugs are made of polypropylene monofilament and have been recalled due to complications and due to their omega 3 fatty acid coating. A number of lawsuits are in progress and are scheduled to take place throughout the next year [28]. Bard's hernia meshes have also been in use for a longer period of time, citing 50 years of clinical experience,

despite them settling the largest hernia mesh lawsuit to date in 2011 of $184 million for around 3,000 cases [27]. All of Bard's polypropylene meshes were found ineffective. Ethicon's Physiomesh is a coated polypropylene mesh that was pulled from the market due to failure to integrate into the body along with other complications. Some of Medtronic's meshes have also been involved in hernia mesh lawsuits.

Reimbursement:

According to one source, the cost for an open hernia repair is between $4000 and $6000. The average percent that a patient would need to pay after insurance would be about 18 percent, or between $720 and $1080. The laparoscopic surgery cost can be slightly higher. It seems that these costs reflect procedures with no mesh, however, and those using mesh were reported to be tens of thousands of dollars. Over all there was a wide range of final costs and amounts that insurance companies were willing to pay among reported procedures [29].

In order to stay competitive with other mesh products on the market, our mesh would have to follow a similar reimbursement process as others. The procedure would include costs for anesthesia, time in the operating room, the incisions made, whether the procedure was laparoscopic or open, and supplies such as the mesh as it would be used. Our product would be eligible for coverage from private and public insurers. Medicare covers about 80 percent of inguinal hernia mesh procedures as long as the procedure is deemed medically necessary. Hernia repair is usually an outpatient surgery, and has a faster recovery time with laparoscopic repair which can minimize costs.

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