Phasix™ Mesh Load Transfer

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Load Transfer:

Mechanism of Phasix™ fully resorbable mesh degradation and tissue integration for a durable repair.

A scientific, evidence-based theory of progressive load transfer

Stephen F. Badylak, DVM, PhD, MD
Deputy Director of the McGowan Institute for Regenerative Medicine

Product Description

Phasix™ Mesh is a resorbable material composed of Poly-4-hydroxybutyrate (P4HB). P4HB is a naturally occurring polymer produced by microorganisms as part of their normal metabolic activities. In vivo, the Phasix™ Mesh material degrades primarily by hydrolysis over a period of twelve to eighteen months. The degradation by-products of P4HB consist of carbon dioxide and water, and therefore have minimal effects upon the surrounding microenvironment. The combination of a naturally occurring polymer, benign degradation products, and slow predictable degradation provide a favorable environment for healing, which is important for constructive and functional tissue remodeling.

Fundamental principles of load transfer

Well established principles of wound repair, tissue development and tissue biomechanics embody the concept of "use it or lose it." Just as Julius Wolff theorized in the 19th century that the structure and composition of trabecular bone changes as a function of applied load[1], the corollary principle for soft tissue is referred to as Davis' Law[2]. Davis' Law states that any soft tissue subjected to mechanical loading will adapt by the addition of more soft tissue at the site to accommodate the load. Stated differently mammalian tissues are programmed to adapt, within limits, to the demands of their environment. Tissues such as collagenous matrix and skeletal muscle, which are present in the abdominal wall, are especially responsive to mechanical loading since their primary function is load bearing.

A large body of preclinical and bench top evidence supports the concept that progressive mechanical loading of tissue stimulates the development of site appropriate strong tissue, that can meet the demands of the local tissue environment. For example, in a rodent model of rat achilles tendon injury, inhibition of mechanical stimulation results in reduced tendon size and impaired strength compared with normal cage activity[3]. In contrast, cyclic mechanical loading of human tendon fibroblasts in vitro induced enhanced secretion of growth factors TGF-B1, PDGF, and bFGF that are known to modulate tendon and ligament healing through stimulation of cell proliferation, differentiation, and matrix formation[4]. Collagen synthesis and extracellular matrix (ECM) turnover is also dramatically increased by physical activity and mechanical loading whereas inactivity markedly decreases collagen turnover in both tendons and muscle[5]. These principles can be used in the design of next generation surgical mesh materials. It is clear that gradual transfer of mechanical load from a surgical mesh material to the host native tissue can stimulate deposition of strong connective tissue that can withstand physiologic demands, whereas rapid transfer can result in the development of an inadequate irregular collagen network incapable of providing long-term load bearing.

The science behind the concept of progressive load transfer is based upon the concept of mechanotransduction. The transfer of mechanical loading includes mechanisms that involve integrins, cytoskeleton, G proteins, tyrosine kinase, mitogen-activated protein kinase, and stretch-activated ion channels[6]. Host (patient) cells are coupled to the surrounding extracellular matrix by cell integrins that are directly coupled to ECM ligands[7]. Integrins are trans-membrane receptors with a head domain connected to either adjacent cells or specific domains of ECM constituents called ligands. The cytoplasmic tail domain is bound to focal adhesion kinase or paxillin. Integrins can be very specific with respect to the ligands within the ECM with which they bind. Stated in practical terms, the mechanical load placed upon a remodeling surgical mesh material can be transferred to the individual cells, and these cells in turn secrete a connective tissue that is able to manage that particular load.

Tissue mechanics are critical factors that should be considered during the development of surgical mesh materials. Tissue mechanics will dictate whether a biomaterial will fail upon implantation, but more importantly, whether it will promote mechanotransduction and subsequent site appropriate tissue remodeling. Thereby, Davis' Law is now being applied to the design and manufacturing of new surgical mesh materials such that a gradual transfer of mechanical load from the surgical mesh to the new host connective tissue occurs[8]

Surgical mesh materials for ventral hernia repair

Surgical mesh materials can be either biologic or synthetic in origin, and both are available for the repair of ventral hernias. Several products have been developed with the concept of load transfer in mind.

For example, Dexon™ (polyglycolic acid) and Vicryl™ are rapidly resorbed materials that degrade by hydrolysis. For Dexon™, up to 80% of the material is essentially resorbed by ninety days after implantation[12], and clinical studies have demonstrated that 29% of incisional hernias can reoccur by one year with a primary suture repair[9]. Vicryl™ consists of a copolymer of lactide and glycolide, both of which degrade by hydrolysis with acidic by-products. Up to 77% of the strength of this polymer is lost by fourteen days in preclinical studies[12] and the mesh is essentially completely resorbed by ninety days post-surgery. Both of these products are associated with a rapid transfer of load from the implanted mesh to the host tissue.

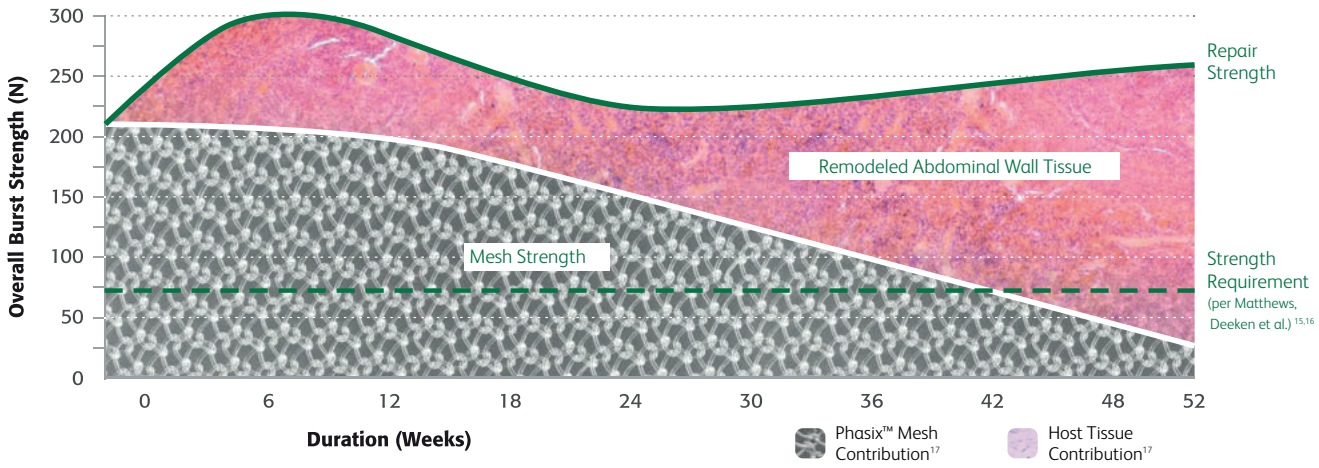
Phasix™ Mesh is monofilament mesh composed of the naturally occurring material, P4HB, described above and based on preclinical testing provides for gradual loss of strength over a twelve to eighteen month period of time. Thus, it provides strength to the repair site with gradual transfer of the load to the newly deposited host tissue (i.e., Davis' Law) for a much longer period of time than other current resorbable materials.

Preclinical studies of Phasix™ P4HB material for hernia repair

Two recent preclinical studies investigated the use of P4HB for hernia repair[10].

In the first preclinical porcine study[10, 11], P4HB was investigated for its ability to reinforce the repair of an experimentally created ventral abdominal hernia. Results showed 100% efficacy with respect to clinical outcome over a 72-week period of time. Evaluation of mesh strength showed a gradual decrease from an initial strength that was 80% greater than the native abdominal wall to GORE® BIO-A® Tissue Reinforcement is a scaffold material that consists of both glycolide and trimethylene carbonate[12]. These materials breakdown into an acid, which in a preclinical model affected the surrounding micro-environment by increasing both inflammation and fibrosis[10]. This material degrades by both hydrolytic and enzymatic processes that require approximately one-hundred-eighty days in vivo[12]. 50% of GORE® BIO-A® Tissue Reinforcement is resorbed by five weeks post-implant and 100% of the GORE® BIO-A® Tissue Reinforcement is resorbed by seven months[13]. This material provides a gradual transfer of load, allowing for adaptation of the host tissue.

Repair strength over time in a 52 Week Preclinical Model[15]



TIGR® Matrix Surgical Mesh is a multifilament mesh product that is manufactured from two separate types of fibers; consisting of a copolymer of polyglycolide and polylactide with polytrimethylene carbonate. The different components degrade in vivo at different rates. The first fiber contributes to strength for seven to fourteen days and the second fiber contributes to strength for six to nine months, respectively[14]. This too is a more gradual transfer of load than Vicryl™ or Dexon™.

a strength that was virtually identical with the native abdominal wall at the 72-week time point. This gradual decrease in strength to normal values was associated with the degradation of the P4HB and a constructive tissue remodeling response.

In a separate preclinical porcine study[10, 12], the ability of P4HB to bridge a full thickness ventral abdominal wall defect was evaluated. The material provided a scaffold for native tissue in growth with significantly greater burst strength and stiffness than native abdominal wall at all time points (6, 12, 26, 52 weeks).

These studies show very promising results for the reinforcement of hernias with the P4HB resorbable surgical mesh. The gradual transfer of load, lack of cytotoxic degradation by-products, and deposition of strong host connective tissue at the repair site are characteristics of an ideal fully-resorbable surgical mesh.

Summary
Surgical mesh materials play an important role in the repair of hernias. The concept of Davis' Law to provide immediate reinforcement and strength while gradually transferring the load bearing responsibilities to the body wall of the patient is of interest when choosing the appropriate mesh prosthetic for soft tissue reinforcement. The end result is the complete degradation of the scaffold and replacement by appropriately strong patient-derived connective tissues.

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This document is Dr. Badylack's opinion.

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Phasix™ Mesh
Phasix™ Mesh. **Indications:** Phasix™ Mesh is indicated to reinforce soft tissue where weakness exists in patients undergoing plastic and reconstructive surgery, or for use in procedures involving soft tissue repair, such as the repair of hernia or other fascial defects that require the addition of a reinforcing or bridging material to obtain the desired surgical result. **Contraindications:** Because Phasix™ Mesh is fully resorbable, it should not be used in repairs where permanent wound or organ support from the mesh is required. **Warnings:** Phasix™ Mesh must not be put in direct contact with bowel or viscera. The safety and product use for patients with hypersensitivities to tetracycline hydrochloride or kanamycin sulfate is unknown. Use of this device in patients with known allergies to these antibiotics should be avoided. The safety and effectiveness of Phasix™ Mesh in pregnant women, pediatric use and neural and cardiovascular tissue has not been evaluated or established. If an infection develops, treat the infection aggressively. An unresolved infection may require removal of the device. **Adverse Reactions:** Possible complications include infection, seroma, pain, mesh migration, wound dehiscence, hemorrhage, adhesions, hematoma, inflammation, allergic reaction, extrusion, erosion, fistula formation and recurrence of the hernia or soft tissue defect. Please consult package insert for more detailed safety information and instructions for use.

Phasix™ Mesh CE-Marked. **Indications:** Phasix™ Mesh is indicated to reinforce soft tissue where weakness exists in patients undergoing abdominal, plastic, and reconstructive surgery in ventral hernia repair and other abdominal fascial defect procedures. **Contraindications:** Because Phasix™ Mesh is fully resorbable, it should not be used in repairs where permanent wound or organ support from the mesh is required. Phasix Mesh is contraindicated for use in the repair of pelvic organ prolapse. Phasix Mesh is contraindicated for use in the treatment of stress urinary incontinence. **Warnings:** Phasix™ Mesh must not be put in direct contact with bowel or viscera. The safety and product use for patients with hypersensitivities to tetracycline hydrochloride or kanamycin sulfate is unknown. Use of this device in patients with known allergies to these antibiotics should be avoided. The safety and effectiveness of Phasix™ Mesh in pregnant women, pediatric use and neural and cardiovascular tissue has not been evaluated or established. If an infection develops, treat the infection aggressively. An unresolved infection may require removal of the device. **Adverse Reactions:** Possible complications may include, but are not limited to infection, seroma, pain, mesh migration, wound dehiscence, hemorrhage, adhesions, hematoma, inflammation, allergic reaction, extrusion, erosion, fistula formation and recurrence of the hernia or soft tissue defect. Please consult package insert for more detailed safety information and instructions for use.

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