

The History of GalaFLEX P4HB Scaffold

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Aesthetic Surgery Journal
2016, S1–S10
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DOI: 10.1093/asj/sjw141
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Abstract

The GalaFLEX Scaffold (Galatea Surgical, Inc., Lexington, MA) for plastic and reconstructive surgery belongs to a new generation of products for soft tissue reinforcement made from poly-4-hydroxybutyrate (P4HB). Other members of this new family of products include MonoMax Suture (Aesculap AG, Tuttlingen, Germany) for soft tissue approximation, BioFiber Scaffold (Tornier, Inc., Edina, MN) for tendon repair, and Phasix Mesh (C.R. Bard, Inc., Murray Hill, NJ) for hernia repair. Each of these fully resorbable products provides prolonged strength retention, typically 50% to 70% strength retention at 12 weeks, and facilitates remodeling in vivo to provide a strong, lasting repair. P4HB belongs to a naturally occurring class of biopolymers and fibers made from it are uniquely strong, flexible, and biocompatible. GalaFLEX Scaffold is comprised of high-strength, resorbable P4HB monofilament fibers. It is a knitted macroporous scaffold intended to elevate, reinforce, and repair soft tissue. The scaffold acts as a lattice for new tissue growth, which is rapidly vascularized and becomes fully integrated with adjacent tissue as the fibers resorb. In this review, we describe the development of P4HB, its production, properties, safety, and biocompatibility of devices made from P4HB. Early clinical results and current clinical applications of products made from P4HB are also discussed. The results of post-market clinical studies evaluating the GalaFLEX Scaffold in rhytidectomy and cosmetic breast surgery demonstrate that the scaffold can reinforce lifted soft tissue, resulting in persistent surgical results in the face and neck at one year, and provide lower pole stability after breast lift at one year.

Accepted for publication July 15, 2016.

Surgeons have used different types of meshes, sutures, and scaffolds in cosmetic surgery procedures for over 35 years. In 1981, Johnson described the use of MARLEX mesh (C.R. Bard, Inc., Murray Hill, NJ) as a sling to support breast tissue during reduction mammoplasties and mastopexies.¹ In this application, the mesh was attached to the second rib, and used to convert the support of the breast tissue from a cutaneous origin to a skeletal origin providing internal support of the breast tissue. MARLEX mesh is made from polypropylene and is not resorbable. Rather, it is a permanent implant and rib attachment methods can cause long-lasting discomfort.

Auclair and Mitz subsequently described the use of a periareolar skin resection technique using a resorbable mesh for scaffold-assisted mastopexy.² They created an internal bra by placing VICRYL mesh (J&J, New Brunswick, NJ) around the anterior surface of the breast gland. Góes has also frequently reported the use of many types of permanent and resorbable

scaffolds in his periareolar mammoplasty procedure using a double skin technique.³ His technique involves dissecting the soft tissue envelope away from the parenchyma, and wrapping the breast parenchyma to produce a breast lining structure that would be less susceptible to ptosis. Góes has specifically noted that meshes with short-term resorption profiles, such as VICRYL mesh, provide early support, but absorption of the mesh after 3 months leads to recurrent ptosis.⁴

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The first synthetic, absorbable fibers for medical applications were developed in the 1970s. Although resorbable fibers have now been used for over 40 years in medical devices, most resorbable fiber-based products degrade too rapidly in the body for use as durable transitory scaffolds. A resorbable polymer that can be used to produce a long-lasting transitory scaffold, and will resorb and leave a strong repair has been elusive until relatively recently.

In 2007 the FDA cleared a new resorbable, high-strength suture made from poly-4-hydroxybutyrate (P4HB), a resorbable polymer with long-term strength retention properties.^{5,6} The clearance was significant because the P4HB suture was the first long-term resorbable suture to reach the market in many years. Once cleared, applications and use of P4HB expanded rapidly on account of its unique properties and excellent biocompatibility. By the end of 2015, there were over 20 additional regulatory clearances for products made from P4HB with intended uses ranging from hernia repair to plastic surgery. GalaFLEX Scaffold (Galatea Surgical, Inc., Lexington, MA), shown in Figure 1A, was cleared for use in the repair, reinforcement, and elevation of soft tissue deficiencies, including use in plastic and reconstructive surgeries.⁷ Over one million patients have been implanted with P4HB-based medical devices in the last 7 years.

The GalaFLEX Scaffold is a macroporous, monofilament long-term implant (Figure 1B) that acts as a lattice for tissue ingrowth, becomes well integrated over time, and resorbs leaving a strong, lasting repair. In this article, we will review the history of the P4HB scaffold starting with the unique properties of P4HB, in vivo performance data, integration, and vascularization of the GalaFLEX Scaffold, early clinical trials, and the current applications of P4HB in wound management, hernia repair, sports medicine, and plastic and reconstructive surgeries.

EARLY DEVELOPMENT OF P4HB

P4HB belongs to a large group of naturally occurring biopolymers, known as polyhydroxyalkanoates (PHAs). PHAs

have been referred to as the fifth class of important, naturally occurring polymers alongside polyisoprenoids, polypeptides, polysaccharides, and polynucleotides.⁸ PHAs are biosynthesized in nature by microorganisms as energy reserve materials that can be stored up and broken down when needed. In this manner, PHAs enable certain microorganisms to regulate their metabolism. It is, however, the thermoplastic properties of PHAs that have attracted significant commercial attention in this class of polymers. Once isolated and purified, PHAs can be processed into many useful products. Unfortunately, PHAs are difficult to chemically synthesize, thus their use remained limited until the development of cost-effective biosynthetic methods.

In the late 1980s, researchers at the Massachusetts Institute of Technology (M.I.T.),⁹ and others,¹⁰ were successful in identifying the pathways used by microorganisms to produce PHA polymers, and developing efficient production systems for their biosynthesis. These efforts led to the development of a fermentation-based system for the production of P4HB, allowing large-scale manufacture of this polymer for the first time. P4HB is produced using *Escherichia coli* K12,¹¹ a microorganism that is the workhorse of the biotechnology industry, and currently used to make biosynthetic drugs like insulin.¹² After its biosynthesis, P4HB is isolated from the microorganism and is obtained in very high purity. This method of production does not employ potentially toxic additives like heavy metal catalysts or cross-linking compounds that are used in the production of synthetic resorbable polymers or cross-linked collagen matrices.

DEGRADATION MECHANISM OF P4HB

In vivo, P4HB is degraded primarily by bulk hydrolysis wherein water molecules diffuse into the polymer, and cleave the polymer chains.¹³ Enzyme-catalyzed hydrolysis is believed to cause a small amount of surface erosion. The dominant bulk hydrolytic pathway, however, results in a predictable steady loss of polymer molecular weight and

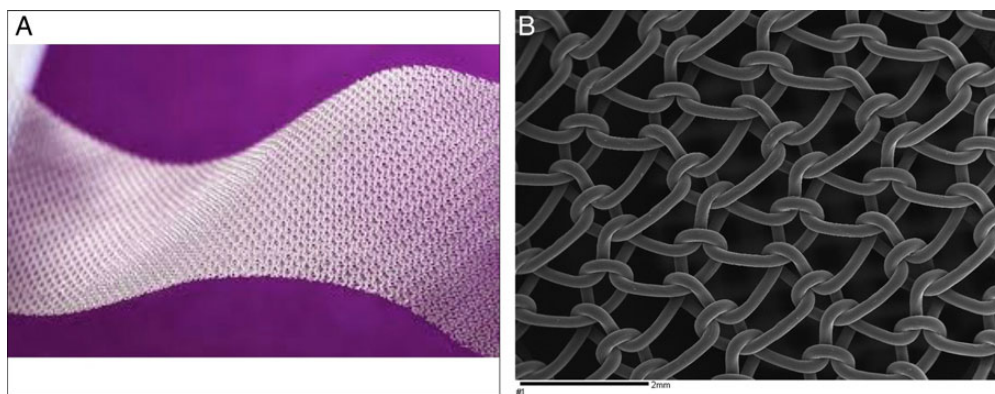


Figure 1. GalaFLEX Scaffold. (A) $10 \times 20 \text{ cm}^2$ GalaFLEX Scaffold and (B) photomicrograph of scaffold showing macroporous, monofilament structure.

decrease of strength retention over time. P4HB degrades into 4-hydroxybutyrate (4HB), a natural metabolite present in humans and other animals, as well as certain foods. In the mammalian body, 4HB is found in a wide variety of tissues, including brain, heart, kidney, liver, lung, muscle, and brown fat.¹⁴ Its half-life of just 27 minutes is relatively fast,¹⁵ and means that 4HB released from a degrading implant of P4HB will be rapidly metabolized. The metabolism of 4HB has been well studied. 4HB is catabolized via the Krebs cycle (also known as the citric acid cycle or tricarboxylic acid cycle), and is broken down in vivo and eliminated as carbon dioxide and water. Consequently, P4HB implants such as the GalaFLEX Scaffold are completely transitory with no polymer metabolites remaining after the degradation process is complete.

MECHANICAL PROPERTIES AND IN VIVO STRENGTH RETENTION OF P4HB

P4HB has a very unique set of properties particularly in comparison to other polymers commonly used in resorbable medical devices, such as polyglycolide (PGA) and polylactide (PLA), which are inherently much stiffer materials. When P4HB is stretched, the mechanical strength of the polymer rises substantially, yet the polymer still remains flexible. In contrast, when PGA or PLA are stretched, the mechanical strength increases, but the polymers become very brittle. As a result, PGA and PLA polymers are typically converted into multifilament yarns, rather than monofilament fibers, in order to maintain flexibility when they are used as sutures or woven/knitted into a textile. In contrast, the properties of P4HB make it possible to produce high strength and pliable *monofilament* fibers that may, if desired, also incorporate an element of elasticity. Monofilament fibers and sutures are often preferred over multifilament fibers because of their smooth surfaces and because they lack microscopic interstices that can harbor bacteria and lead to increased risks for infection.

Table 1. Comparison of Monofilament Fiber Properties (data from Williams and Martin)¹⁶

Fiber	Property	Diameter (μm)	Tensile Strength (MPa)	Elongation at Break (%)
P4HB	Resorbable	154	728	35
PDS II	Resorbable	166	538	39
PROLENE	Permanent	143	610	31

As shown in Table 1, P4HB fibers can be prepared with tensile strengths that exceed not just those of other resorbable monofilaments such as PDS II sutures (J&J, New Brunswick, NJ), but also permanent ones made from polypropylene, like PROLENE sutures (J&J, New Brunswick, NJ).¹⁶

Until the introduction of P4HB, synthetic monofilament and multifilament absorbable sutures generally had relatively short strength retention in vivo. For example, VICRYL multifilament sutures typically lose 50% of their initial strength within 3 weeks, and are completely resorbed between 56 and 70 days. PDS II monofilament sutures degrade slightly slower, but have little residual strength after approximately 8 weeks. MONOCRYL monofilament sutures (J&J, New Brunswick, NJ) degrade even faster than PDS II sutures with about 50% loss of strength at 1 week, and complete resorption by 91 to 119 days. Of course, these polymers were primarily designed for use as sutures in wound healing, and not for use as scaffolds for long-term reinforcement, which may require a longer strength retention profile to allow native tissue ingrowth and remodeling.

In contrast to VICRYL, PDS II, and MONOCRYL fibers, P4HB fibers retain their strength longer in vivo, and their degradation has been extensively studied in a variety of animal models. Degradation and strength retention of P4HB sutures and scaffolds have been measured in subcutaneous rabbit models as well as porcine abdominal wall models.¹⁶⁻¹⁸ The GalaFLEX Scaffold retains approximately 70% of its strength after 12 weeks in vivo and is essentially fully resorbed by 18 to 24 months.

The ability to make P4HB fibers with superior strength and flexibility enables the production of knitted or woven, monofilament textile products, such as the GalaFLEX Scaffold that provide immediate strength for soft tissue reinforcement during the initial healing phase, and lattice structures that allow tissue ingrowth and remodeling over time as described later in this article in the Tissue Ingrowth section. The successful transfer of load bearing from the implant to the tissue enables a long-term, durable result.

Table 2. Ball Bursting Strength of GalaFLEX Scaffold Measured Using a 1 cm Probe Compared to Tissue of the Human Abdominal Wall also Measured with a 1 cm Probe

Sample Description	Bursting Strength (kgf)
External oblique abdominal muscle aponeurosis ^a	9.82 ± 3.6
Internal oblique abdominal muscle ^a	5.27 ± 2.5
Transversalis fascia ^a	1.09 ± 0.9
Peritoneum and preperitoneal tissue ^a	4.45 ± 2.1
GalaFLEX scaffold	22

^aData taken and calculated from Wolloscheck et al.¹⁹

To form the GalaFLEX Scaffold, P4HB fibers are knitted into a porous textile (Figure 1B). The fibers provide strength, while the pores between the fibers allow space for tissue in-growth. As a textile, the GalaFLEX Scaffold has a burst strength that is stronger than the tissue layers in the human abdomen (Table 2).¹⁹ Since the pores of the GalaFLEX Scaffold are fairly large, the scaffold can be classified as macroporous. This design may reduce surgical complications as compared to scaffolds with a microporous, multifilament design.²⁰

SAFETY/BIOCOMPATIBILITY OF P4HB

P4HB products have been used in over one million surgeries. Products implanted have included: (1) sutures for wound closure, abdominal wall closure, and tendon repair; (2) meshes for hernia repair; (3) scaffolds and devices such as the GalaFLEX Scaffold for plastic and reconstructive surgery; and (4) scaffolds like the BioFiber Scaffold (Tornier, Edina, MN) for rotator cuff and tendon repair.

The initial regulatory submission to the FDA for sutures made from P4HB included a complete profile of standard biocompatibility testing of both the polymer and the devices according to the International Standard ISO-10993 “Biological Evaluation of Medical Devices Part-1: Evaluation and Testing.” The results from cytotoxicity, irritation and sensitization, systemic toxicity, genotoxicity, hemolysis, and subchronic and chronic implantation supported the biocompatibility of the device.¹⁷

TISSUE INGROWTH

The GalaFLEX Scaffold is designed to provide immediate soft tissue support, allow robust tissue ingrowth, and resorb in a predictable and steady manner. As described in

this section, the ingrown tissue remodels and gains strength over a period of months. Therefore, it is important that the scaffold retains sufficient strength during the tissue regeneration process, such that the critical strength loss as the scaffold degrades is offset by tissue ingrowth. In this way, the mechanical load initially borne by the scaffold can be transitioned to the new well-vascularized tissue.

Two extensive *in vivo* studies have been performed using P4HB monofilament scaffolds in porcine abdominal wall hernia repair. One study focused on the strength of the repair itself, and the other study examined the tissue remodeling process and strength retention of the repair. Martin et al evaluated a P4HB scaffold in a porcine hernia repair model, and demonstrated successful transfer of load from the P4HB scaffold to the ingrown tissue, such that the repair strength was comparable to native tissue. Importantly, the repair site gained strength during tissue remodeling as the scaffold resorbed.¹⁸

Deeken et al undertook an extensive histological and mechanical strength investigation of hernia repair of full thickness defects in Yucatan minipigs with two different P4HB monofilament scaffolds, a flat mesh and a plug design.²¹ The study demonstrated that implantation of both scaffolds resulted in vascularized tissue that remained patent throughout the study, as well as typical early wound healing and later tissue remodeling responses. The resulting repairs had high initial strength and retained greater strength than native abdominal wall tissue over the entire 52-week period. Taken together, these two studies demonstrate *in vivo* strength retention resulting from robust tissue ingrowth with concomitant vascularization, and a prolonged surgical result without the use of a permanent supportive implant (Figure 2).

Human explants of the GalaFLEX Scaffold provide additional evidence that the GalaFLEX Scaffold promotes robust

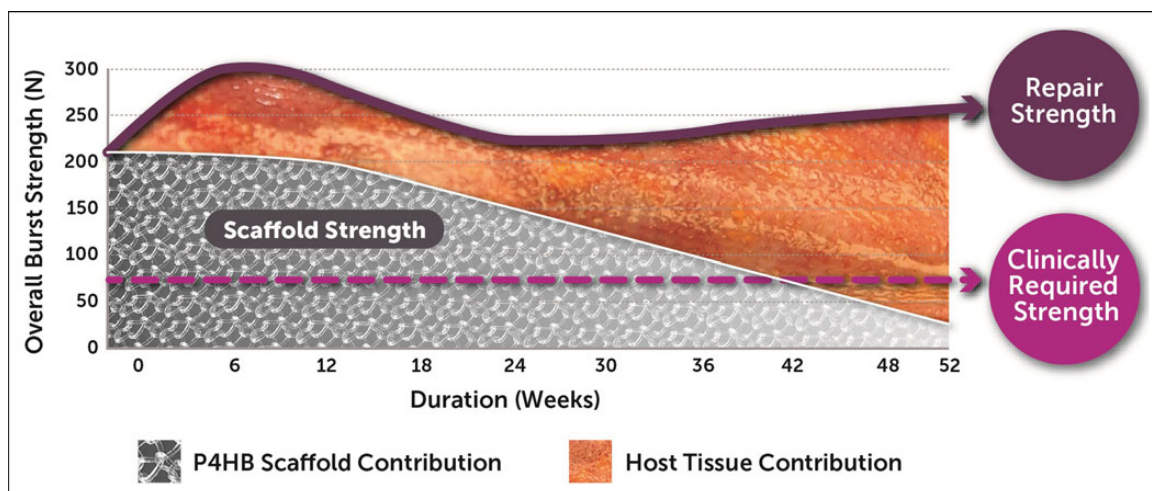


Figure 2. Remodeling of P4HB mesh to provide a strong repair in a porcine hernia repair model (derived from data in References #18, 19, 21, and 28). Adapted from: <https://www.davol.com/product-listing/sp/phasix-mesh>.

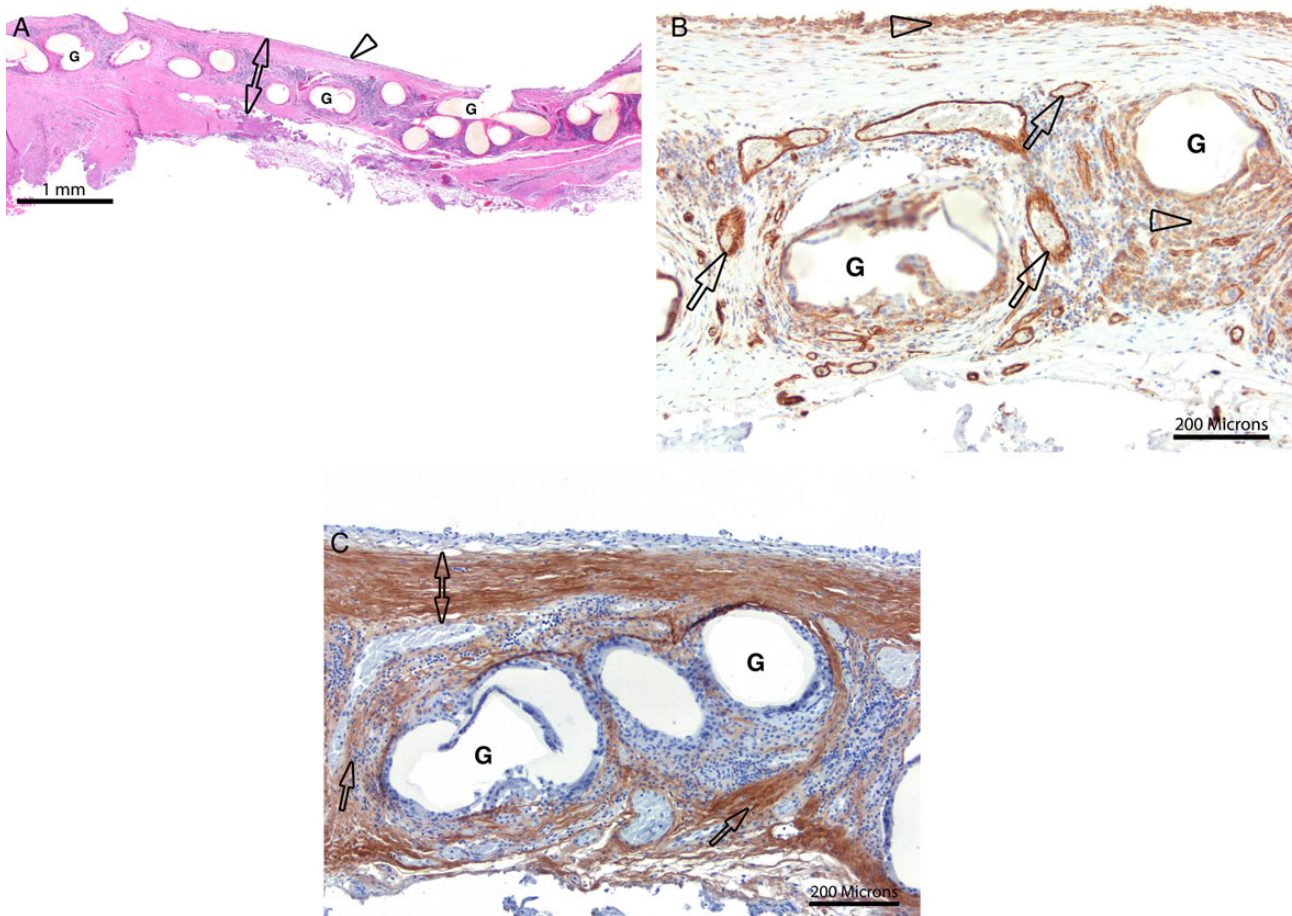


Figure 3. Representative histological cross-sections of the GalaFLEX Scaffold demonstrating tissue ingrowth, vascularization, and the formation of mature connective tissue at 6 weeks post implantation. Microscopic analysis of human tissue containing the GalaFLEX Scaffold (denoted as “G”) explanted from a healthy mastopexy site at 6 weeks. (A) H&E stain showing tissue ingrowth into the GalaFLEX Scaffold. (B) CD31 stain showing neovascularization of new tissue formed around the GalaFLEX Scaffold. (C) Collagen type I stain showing deposition of mature type I collagen throughout the GalaFLEX Scaffold. The double-headed arrow shown in Figure 3A indicates the thickness of the diffuse connective tissue ingrowth with integration of the scaffold into the newly formed capsule. Figure 3B shows a dense network of vascularized channels within the connective tissue infiltrating the GalaFLEX Scaffold (the arrows in Figure 3B indicate the positions of endothelial cells lining the vascular channels through the tissue, and arrowheads show the location of cells producing a mild inflammatory response to the scaffold as it degrades). The formation of mature type I collagen in the 6-week explant is shown in Figure 3C with double-headed arrows showing type I collagen formed along the GalaFLEX Scaffold, and arrows showing type I collagen formed in the pores of the scaffold.

vascularized tissue ingrowth. Explants from breast tissue show robust ingrowth into the pores of the scaffold by six weeks after surgery. These samples were judged to have excellent tissue integration and biocompatibility (Figure 3).²² Microscopic analysis revealed extensive connective tissue integration of the GalaFLEX Scaffold throughout the sample with newly formed vascularized connective tissue ranging in thickness from 0.75 to 1.5 mm, which was thicker than the initial thickness of the scaffold (0.6 mm). The GalaFLEX Scaffold was clearly embedded within a mature fibrous and richly vascularized connective tissue, and only a mild inflammatory response consistent with a low-grade foreign body response typical for any implant was apparent.

Breast tissue explants from a patient seven months post-surgery further delineate ingrown tissue maturation and

biocompatibility of tissue abutting the GalaFLEX Scaffold.²³ Histopathology performed on an explant from a patient 7 months after a bilateral standard mastopexy with placement of GalaFLEX Scaffold, shows that the scaffold was embedded within a mature fibrous and richly vascularized connective tissue, with tissue remodeling ongoing as evidenced by residual deposition of type III collagen in the interstitium. The thickness of the mature fibrous connective tissue in this sample is over 3 mm (see double-headed arrow in Figure 4A), compared to the original thickness of the scaffold (0.6 mm). Figure 4B also shows further development of the tissue with the formation of well-differentiated blood vessels in the connective tissue matrix evident from alpha-smooth muscle actin (α -SMA) staining. The presence of integrated type I collagen in the 7-month explant is shown

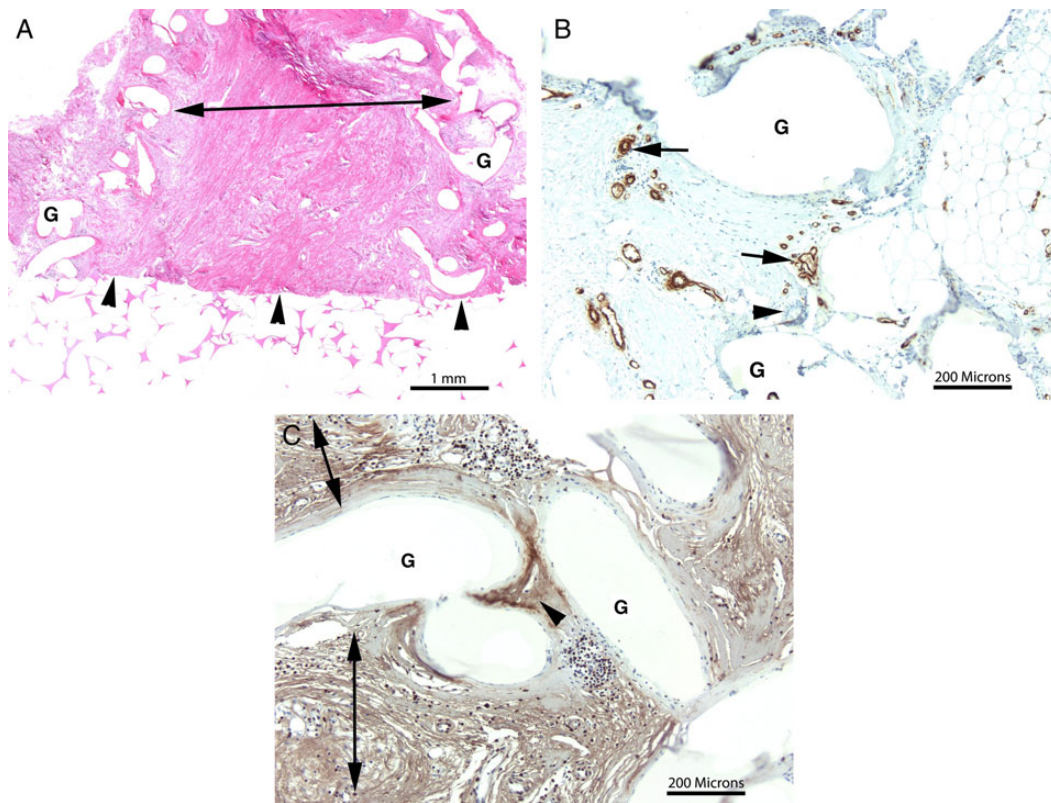


Figure 4. Representative histological cross-sections of the GalaFLEX Scaffold at 7 months post-implantation demonstrating increased thickness of the connective tissue, and maturation of the tissue. Microscopic analysis of human tissue containing the GalaFLEX Scaffold (denoted as “G”) explanted from a mastopexy site at 7 months. (A) H&E stain showing a thick mature fibrous connective tissue embedding the scaffold. (B) α -SMA immunohistochemical stain showing neovascularization with differentiated blood vessels in a connective tissue matrix. (C) Collagen type I stain showing deposition of abundant mature type I collagen throughout the connective tissue and infiltrated in the pores of the GalaFLEX Scaffold. The double headed arrow in Figure 4A shows that the thickness of the mature fibrous connective tissue is over 3 mm, and the arrowheads show the sharp edge of the tissue biopsy or surgical resection. The arrows in Figure 4B show SMA + cells forming the wall of well differentiated blood vessels in the connective tissue matrix, and the arrowhead shows glandular ducts (SMA-). The double-headed arrows in Figure 4C show intervening type I collagen between the GalaFLEX Scaffold fibers, and the arrowhead shows type I collagen around and in direct contact with the GalaFLEX Scaffold.

in Figure 4C with the double-headed arrows showing intervening type I collagen between the GalaFLEX Scaffold fibers, and the arrowhead showing type I collagen around and in direct contact with the GalaFLEX Scaffold. Similar to the results at 6 weeks, the inflammatory response remained minimal to mild and no adverse reaction to the scaffold was present. Biocompatibility was reported to be close to optimal with complete integration of the scaffold, thus, like the result from the abdominal wall study, the pathology indicates well-vascularized ingrown tissue presumed to be capable of continued support of the surgical result.²³

EIGHT YEARS OF HUMAN USE OF P4HB DEVICES

GalaFLEX Scaffold is the latest entrant in an innovative series of P4HB medical devices that have been cleared for

various indications. While the range of applications for these P4HB devices is fairly diverse, each application demands a solution that provides prolonged strength retention for a successful outcome. This requirement is met by the unique properties of P4HB fibers that not only offer high strength and prolonged strength retention, but also allow tailored engineering of devices, for example, with optimum flexibility, porosity, pliability, and shape.

MonoMax Suture

MonoMax suture (Aesculap AG, Tuttlingen, Germany) was the first commercial product produced from P4HB, and was launched in 2009 by B. Braun Surgical.¹⁷ MonoMax suture is made from P4HB monofilament, albeit with properties engineered specifically for soft tissue approximation. The MonoMax suture is stronger, and retains strength longer,

than a PDSII suture. Initially, three sizes of the MonoMax suture, namely USP 2-0, 0, and 1 were commercially launched, available dyed or undyed. These sutures were developed specifically for abdominal wall closure where high strength and prolonged strength retention are needed. In vivo, these sutures retain at least 50% of their initial tensile strength after 3 months. Furthermore, these suture fibers have a very low tensile modulus, about one-third of the value of PDSII sutures, which makes the MonoMax sutures very pliable and flexible. In fact, the MonoMax sutures are the most pliable monofilament sutures currently available. As well as having improved pliability, the MonoMax abdominal sutures have also been engineered with an element of elasticity to prevent the suture from cutting, or cheese wiring, through the tissue. The small amount of elasticity allows the suture to stretch and recover very slightly under stress, for example, when there is increased abdominal pressure, and as a result the elasticity may reduce wound dehiscence and tearing of tissues.

MonoMax sutures were first implanted 8 years ago when 150 patients were recruited for the ISSACC clinical trial to determine the safety and effectiveness of the MonoMax suture for abdominal wall closure after primary midline laparotomy.²⁴ The study was a prospective, multicenter, single-arm trial that was compared to a historical control. The primary endpoints of the trial were typical for an abdominal wall study and included reoperation due to burst abdomen and wound infection until the day of discharge. The secondary endpoints were the rates of incisional hernia 1 and 3 years after surgery, wound infection, complicated healing, length of hospital stay, and safety parameters.

Data from the ISSACC trial were compared to a group of 141 patients in a related study, the INSECT trial,²⁵ where abdominal wall closure was performed with a polydioxanone (PDO) suture, either PDSII or MonoPlus suture (Aesculap AG, Tuttlingen, Germany). For the primary endpoint, 11.3% of patients receiving PDO sutures experienced wound infection or burst abdomen until the day of

discharge compared to only 7.3% of patients receiving the MonoMax sutures.²⁶ The duration of hospital stays was similar in both the PDO and MonoMax groups; however, the rate of incisional hernia at one year for patients that received the MonoMax suture was 14% compared to 21.3% for PDO sutures.²⁶ The investigators concluded that the MonoMax suture is safe and effective for abdominal wall closure, and the results of the ISSACC study were used to support European regulatory approval of MonoMax suture.

The unique properties of P4HB make it possible to produce the most pliable monofilament sutures, and the low tensile modulus of the polymer means that the MonoMax sutures have excellent knot strength and security. Recognition that a MonoMax suture may be secured with fewer knot throws than other sutures, as well as other considerations, led B. Braun Surgical to develop smaller sizes of the MonoMax suture for use in plastic and reconstructive surgery. This effort resulted in the introduction of a size 3-0 MonoMax suture that can be secured with just 4 to 5 throws compared to 6 throw knots typically used by surgeons for other monofilament sutures.¹⁷ As well as reducing operating time, decreasing the size of the knot bundle and using a softer suture fiber can reduce knot palpability and the possibility of irritation arising from the suture ends. These features of the MonoMax suture, which are important when knot bundles are close to the surface of the skin, could help to improve patient satisfaction in procedures such as facial plastic surgery. The size 3-0 MonoMax suture, like the larger sizes, is also slightly elastic making it possible to apply tension in lift procedures, as well as closures, and the flexibility of the suture may also help facilitate suturing when radii are particularly tight.

BioFiber Scaffold for Tendon Repair

Introduced in 2011, the BioFiber Scaffold, shown in Figure 5A, is the first orthopedic soft tissue scaffold made from P4HB.²⁷ It is a porous textile construct of

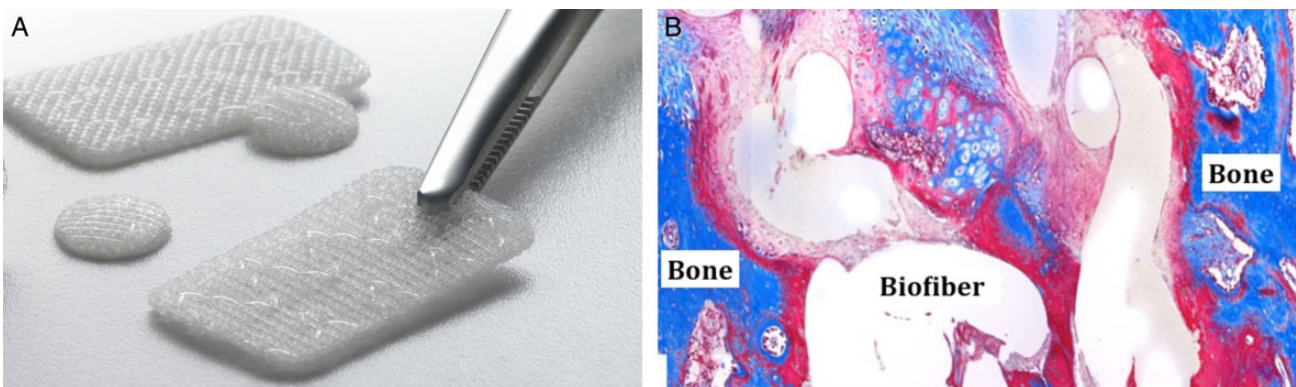


Figure 5. BioFiber Scaffold for orthopedic soft tissue repair. (A) Image of scaffolds. (B) Trichrome stain showing bone has grown completely through scaffold. Images courtesy of Tornier, Inc.

monofilament fibers with strength retention of approximately 50% at 3 months. It is designed to distribute the load of a tendon repair while the tissue is remodeling. The BioFiber Scaffold is manufactured using a leno weave of P4HB fibers that produces a dimensionally stable dense weave of fibers about 1 mm in thickness. This construction is well suited for tendon repairs, and may be used for soft tissue reinforcement as an overlay while at the same time providing a lattice for tissue ingrowth. The scaffold, like the MonoMax suture, incorporates a small element of elasticity, but is designed to stimulate remodeling and tissue ingrowth. A representative histological cross-section at a tendon to bone re-attachment site is shown in Figure 5B demonstrating the scaffold's capacity to facilitate: (1) new bone grown completely through the porous scaffold; (2) formation of Sharpey's fibers; and (3) tendon ingrowth. Applications of the scaffold have included its use for rotator cuff repair, Achilles tendon repair, peroneal tendon repair, quadriceps tendon repair, biceps muscle rupture repairs, and plantar fascia augmentation.

Phasix Mesh for Hernia Repair

The unique properties of P4HB have made it possible to develop fully resorbable scaffolds for hernia repair that allow constructive and functional tissue remodeling at the repair site as previously described under "Tissue Ingrowth." Launched in 2013 by C.R. Bard (Murray Hill, NJ), the Phasix Mesh (C.R. Bard, Inc., Murray Hill, NJ) is made by knitting P4HB monofilament into a fully resorbable scaffold that rapidly incorporates tissue.¹⁸ The resorbable mesh has been designed to provide the repair strength of a synthetic mesh but with the remodeling

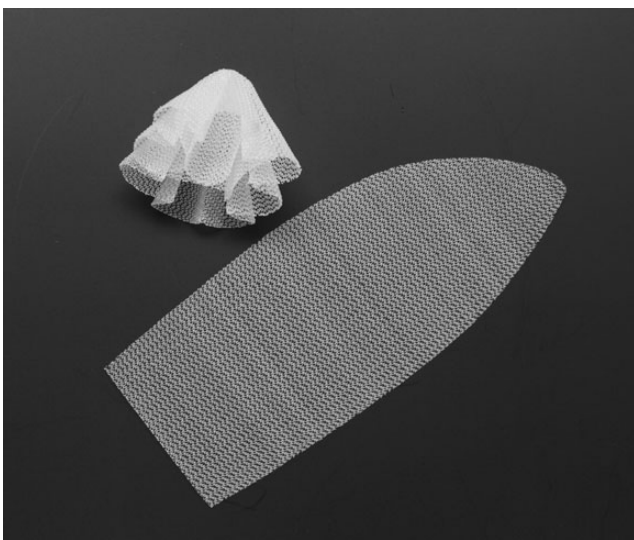


Figure 6. Phasix Plug and Patch made from P4HB for tension-free inguinal hernia repair.

characteristics of a biological material. Over a period of approximately one year, Phasix Mesh is remodeled and replaced with functional tissue that provides a strong and lasting repair.²⁸

Preliminary results of a prospective clinical trial of the Phasix Mesh in 112 high-risk hernia repair patients have recently been reported for the first 50 patients.²⁹ Because the study was meant to assess the performance of the mesh in difficult cases, the inclusion criteria for participation in the trial were: (1) primary ventral, incisional or recurrent (not to exceed 3) incisional hernias undergoing retrorectus or onlay repair; (2) one or more comorbid conditions; (3) hernia size $> 10 \text{ cm}^2$ and $< 350 \text{ cm}^2$; and (4) CDC Class I (clean) wound. Of the initial patients, 32 underwent a retro-rectus repair, 17 an onlay repair, and 1 a preperitoneal repair. At 6 months, pain VAS scores had decreased from a mean value of 4.51 to 1.26. The study investigators concluded that early recurrence with Phasix Mesh was rare, and pain scores improved following hernia repair.

Since the initial launch of the Phasix Mesh, additional P4HB devices for hernia repair have been added to the product line. The Phasix Plug and Patch, shown in Figure 6, offers the benefits of a tension-free pre-peritoneal repair for inguinal hernia repair, but without the placement of permanent foreign material. This option could reduce the risk of chronic pain attributed to damage of sensory nerves and mesh inguinaldynia.

The most recent entrant in the product line is the Phasix ST Mesh (C.R. Bard, Inc., Murray Hill, NJ) for hernia repair. This mesh incorporates a hydrogel barrier on one side of the mesh, based on the Sepra technology (Genzyme Corporation, Cambridge, MA), to minimize visceral tissue attachment to the mesh during intraabdominal placement. On the other side of the mesh, a porous lattice structure of P4HB monofilament allows tissue ingrowth, and incorporation of the repair device. In vivo the hydrogel barrier is resorbed within 30 days, and replaced with a new peritoneal layer by 12 weeks. Remodeling of the Phasix ST mesh continues after implantation, and by 48 weeks the mesh has been remodeled and replaced with mature functional tissue.³⁰

GalaFLEX Scaffold

Initial studies leading to the launch of the GalaFLEX Scaffold for use in plastic and reconstructive surgery started with human use in facelift and was quickly followed with use in cosmetic breast surgeries. The early use in facelift was followed by a prospective, multicenter, post-market study evaluating the use of the GalaFLEX Scaffold to reinforce the lifted and/or imbricated superficial musculoaponeurotic system (SMAS) in 14 patients undergoing rhytidectomy.³¹ The study assessed physician satisfaction based on ease of product use and successful reinforcement,

as well as patient satisfaction. In the study, there was one minor complication (out of 28 implants) that was repaired using an in-office procedure. Overall, patient satisfaction was very high at 30 days after surgery, and remained high out to one year. Surgeon satisfaction was also reported to be high with maintenance of the surgical results in the face and neck at one year. Publication of the full results of this study is expected in the future.

Concurrent with human use, a cadaveric study was undertaken to show the mechanism of reinforcement of the SMAS when using the GalaFLEX Scaffold.³² Samples of SMAS tissue were harvested and dissected in half. The tissue was re-approximated using a suture-only repair as a control or augmented with a sutured onlay of the GalaFLEX Scaffold. Tensile testing of the repaired tissue demonstrated a significant increase in tissue breaking strength for the repairs augmented with the GalaFLEX Scaffold compared to suture-only repairs. The SMAS reinforced by the P4HB scaffold provided not only superior strength results, but also more consistent results in tensile load-bearing quality despite a wide variety of cadaveric tissue strengths. The investigators concluded that reinforcement of the SMAS with a P4HB scaffold would provide a more consistent and long-lasting repair in patients undergoing rhytidectomy.

A prospective, multicenter, post-market study was initiated in July 2012 to assess physician preference in the clinical performance of the GalaFLEX Scaffold in soft tissue reinforcement during elective cosmetic plastic surgery to the breast, in particular mastopexy without augmentation (ie, breast reduction procedures). The primary endpoint of this study is surgeon satisfaction with the surgical implantation/usage of the GalaFLEX Scaffold in elective plastic surgery to the breast at one year. The secondary endpoint is measuring the technical performance of the GalaFLEX Scaffold at one year by evaluating the resolution of ptosis based on the change in nipple to IMF distance and sternal notch to nipple distance pre- and post-surgery measured using a 3-dimensional imaging system (Canfield Imaging Systems, Fairfield, NJ). Although results are not yet published, the investigators reported being impressed by the lower pole stability, particularly in view of the larger breast patients included in this first set of patients (with mean post-surgical volume of 477 cc). One year after surgery, the distance between the sternal notch and the lowest point on the breast was reported to remain relatively stable changing only by an average of 13.5 mm or 5%.³³ Most of this stretch (10 mm) occurred in the first 3 months following surgery indicating that the GalaFLEX Scaffold reduced breast stretch after post-surgical swelling had dissipated. Furthermore, no statistically significant changes were found in the distances from the sternal notch to the nipple, and the nipple to the lowest point on the breast, during the last 9 months of the first year following surgery, and nipple projection remained relatively constant for the first 3

months with no statistically significant changes for the last 9 months. This initial data appear to provide evidence that soft tissue reinforcement by the GalaFLEX Scaffold prevents pseudoptosis.

CONCLUSION

P4HB belongs to a class of naturally occurring polymers, and has a unique set of properties that have resulted in the introduction of a new class of innovative, fiber-based products for soft tissue repair. Fibers of P4HB are characterized by their high strength, prolonged strength retention, pliability, and flexibility, and can be readily converted into scaffolds that become well integrated in vivo. The pores of the scaffolds are rapidly invaded with well-vascularized tissue. Ultimately, the scaffold is resorbed and the new healthy tissue provides a strong durable repair. In a relatively short period of time, the properties of P4HB fibers have enabled the development of a completely new generation of surgical products with the GalaFLEX Scaffold being the most recent entrant.

Disclosures

Dr Williams is a Consultant to Tepha, Inc. and a member of the Tepha Board of Directors. Dr Martin is the Chief Scientific Officer of Tepha, Inc. Dr Moses is a Consultant to Tepha, Inc. and is the Founder of Galatea Surgical, Inc. Galatea Surgical, Inc. is a wholly owned subsidiary of Tepha, Inc.

Drs. Williams, Martin and Moses are consultants or employees of Tepha, Inc. and its wholly owned subsidiary Galatea Surgical, Inc. (Lexington, MA), which manufacture and distribute P4HB products.

Funding

This supplement was funded by Galatea Surgical, Inc. (Lexington, MA), the Musculoskeletal Transplant Foundation, Mentor (Irvine, CA), and the Musculoskeletal Transplant Foundation (Edison, NJ).

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