Regenerez®: How the Incorporation of Regenerative Materials Will Advance Biomedical Textiles

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In the context of biomedical textiles and their use in medical devices, it is important to understand the evolution of biomaterials and how the next generation will enable the body to heal itself. The historical use of textiles in surgical procedures and wound healing closely parallels the greater story of biomaterials. In broad terms, there are four generations of biomaterials and biomedical textiles, with the first two generations focused primarily on repairing and recovering from an injury, defect or condition and the last two focusing on regeneration of tissues. Generally, the first three generations elicit a chronic immune response; the body sees these materials as foreign and tries to eliminate them. This can cause a host of issues, from excess inflammation and scarring to outright implant rejection.

The fourth-generation biomedical textile, which will be made possible with the adoption of advanced biomaterials, discourages this harmful inflammatory response and encourages regenerative healing. The levels of work required to achieve this range from bench top laboratory experiments to human clinical trials.

To explore the recent trends and the future direction for the development and commercialization of biomedical textiles in regenerative medicine, it is necessary to look at some areas in which their uses are expanding as well as an ongoing success story in which a material is moving from bench top to market. This paper reviews the use of biomedical textiles in light of the generational scheme of biomaterials, outlines crucial success factors for bringing projects out of university labs and into commercial use, and discusses how Secant Medical's advanced biomaterial, Regenerez®, fits within this evolution.
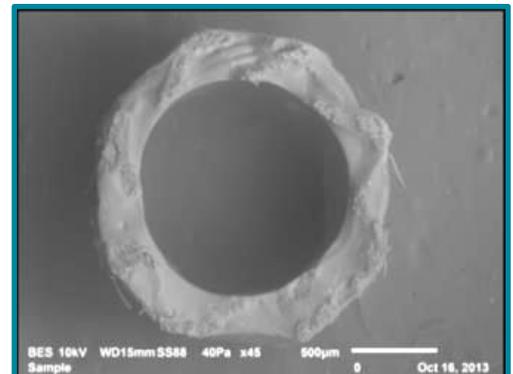
Due to the wide range of physical properties of Regenerez®, there are multiple potential applications for this next-generation bio-elastomer provided by Secant Medical. Pictured above is an example of a hollow lumen structure, a PGA braid coated with a PGS film.

Textile Evolution

Since the times of the ancient Egyptians and Aztecs, sutures composed of various natural materials have been used to close wounds, and by the 1930s, synthetic polymers became available for use in medical applications. In this first generation of medical textile materials, which lasted from the beginning of recorded history to the early 20th century, the focus was simply to create a material that held an injury in place and provided time to heal. Ideally, the goal was to create an inert material. There was little consideration as to the nature of breakdown products formed from the degradation of a suture, for example, if it degraded at all. In fact, many of the animal-based sutures did degrade, while most synthetics did not. Nevertheless, selection of the best first-generation materials hinged on whether they:

- Were unlikely to cause toxic effects in the body

- Maintained mechanical properties after implantation, including possessing good resistance to breakdown and degradation

It was not until the second generation of biomaterials, which emerged in the 1960s and 1970s with the widespread use of polyglycolic acid (PGA) and polylactic acid (PLA), that developers gave consideration to what happens to degradation products. This was a significant improvement over the first generation of biomedical textile materials, which came about as a result of the first major collaborations between physicians and engineers for the purpose of creating medical materials. Previously, engineering materials from other fields were adopted into medical use. Instead of remaining behind after healing had resolved, sutures and other devices made from these materials were designed to break down purposefully. Unlike the case of cat gut sutures, where the degradation products were largely uncontrolled and somewhat poorly understood, PGA and PLA broke down into acids that were part of the normal metabolism of cells. Ultimately, they would enter their appropriate metabolic pathways and break down further until they were released as carbon dioxide from the lungs. Additionally, the second generation of biomaterials introduced the term "bioactive" to mean a material that integrates with tissue through chemical bonding and physiological integration.[1] Often, the degradation products from resorption of the material contribute to this integration by having local cellular effects that facilitate tissue in-growth.

As with the case of first-generation materials, problems with integration were not completely solved in the second generation. These biomaterials, like all others, are considered to be invaders by the natural immune system, which reacts accordingly based on the location of the implanted material and its geometry. All biomaterials cause an acute immune response to some extent, and it can range from mild to severe. In the case of resorbables such as PGA and PLA, the reaction can resolve and does not always proceed to a chronic stage. However, in cases in which that does happen, or where the acute immune reaction is severe, the implant can be compromised and function impaired.

Devices made from resorbable materials generally do not need to be removed post-healing, as compared with many first-generation materials, most of which are capable of eliciting a chronic inflammatory response to the point in which removal is required. Overall, second-generation biomaterials interact meekly with the body's natural biological processes; they are designed to interfere as little as possible, and then disappear.

The third generation of biomaterials incorporates release agents that have physiological effects on tissue at a molecular level. These hybrid materials may be both bioactive and resorbable, and include products such as strings of gentamicin-loaded beads for fighting osteomyelitis (available in European markets) and antibiotic-releasing knitted surgical meshes (widely available in the United States). However, there are still questions about what happens to devices that release active agents once they complete their release cycles. In cases of antibiotic-releasing devices, this can mean giving off dwindling doses of antibiotics, which can encourage drug

resistance. However, antibiotics are not the only releasable agents included in this generation of materials. Other examples include devices loaded with growth factors such as Platelet Derived Growth Factor (PDGF) for enhanced tissue healing, especially in dental applications.

The fourth generation of biomaterials promises to raise biomaterial interactions to the next level: the repair, recovery, and regeneration of damaged tissue by enabling the natural biological processes for healing. This generation incorporates all previous features but also has the unique ability to actively participate in the healing process through direct molecular surface interaction with the treated site. For example, materials that preferentially attach to specific types of integrin receptors on cell membranes can encourage cell attachment by specific phenotypes. Moreover, the surfaces of these materials may change over time to have the ability to alter the cell motility and differentiation during periods of tissue in-growth. These features can guide inflammation to reduce its length or direct it within specific areas, rather than simply minimizing it. All the while, these materials retain bioactivity and resorption properties when necessary. In fact, the resorption is much more controlled and tuned to the events in the surrounding tissue. This can be achieved with multiple layers of materials, such as textile fibers with a "core-sheath" construction made from two or more materials with different degradation profiles. A slow-resorbing material on the outside of the fiber, for instance, can allow tissue in-growth to become established while quickly allowing the textile to erode once the tissue is in place, as the inner core is composed of a fast-resorbing material. This basic function would work in concert with some ability of the material to influence the surrounding tissue through direct geometric or molecular action.

Modern Biomedical Textile Formation

An important aspect in all generations of medical textiles is their ability to be formed into scaffolds for tissue replacement. Since textiles are porous by nature, the manipulation of pore size has been a central feature in medical textile development, primarily to optimize the conditions necessary for a specific application. For any given biomedical textile design, it is important to tune the material's structure for the application. In instances where in-growth is desired, the appropriate pore size and architecture must be present. Conversely, in situations in which in-growth is detrimental, the material must act as a barrier.

Although there are conflicting reports in the literature regarding optimal pore sizes and geometries, especially for bone tissue, as well as differences in the methodology for determining desired values of these parameters for specific cell types, pore architecture in textiles can be controlled.[2,3] Knitted fabrics can have complex networks of interconnected pores of various sizes to accommodate the flow of nutrients and the movement of cells through the matrix. This mass flow can be aided or inhibited through altering patterns of the knitted structure to have bimodal or even trimodal average pore distributions. Additionally, spacing between fibers in a
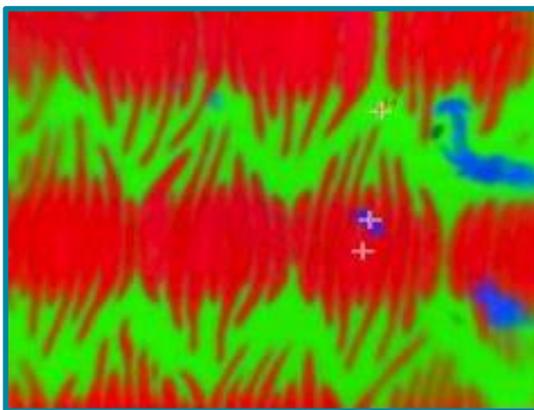
woven fabric can be pre-determined and implemented on a computerized loom. Due to the nature of weaving processes, those pores are generally square-shaped and not randomly distributed throughout the textile matrix. Controlled pore size and distribution constitute controlled scaffold architecture. Together, these parameters in turn control fabric or scaffold density.

The density of a textile can be increased to the point in which pores are too small to allow the passage of cells, and even liquids such as blood. Conversely, the pore size can be opened up to produce a loose mesh. "Blood-tight" woven fabrics are a common component in vascular prostheses and cardiovascular devices, such as heart valves, which contain at least one biomedical textile component (usually the skirt around the implant that acts as the interface between the edge of the valve and the tissue). From a generational perspective, these parameters serve to maximize the repair and recovery of tissue by directly replacing structures in the body in a semi-permanent fashion. This puts them squarely in the first generation.
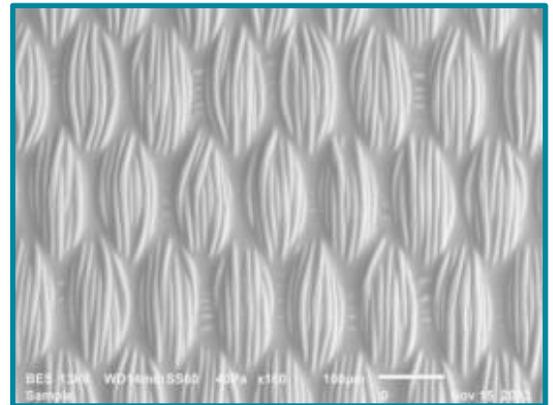
Creating Regenerative Textiles from New Material

The leap from a tailored scaffold that minimizes interference with the natural healing process to a functional scaffold that actively participates in tissue regeneration is the critical element that elevates a medical textile structure into the fourth generation. This tissue regeneration capability can become part of the design in several ways. The textile or device can be constructed entirely from the new material, or more likely, consist of a composite system of materials acting in concert. Regenerative capabilities can also be achieved through the use of bio-functionalized coatings. By coating a porous scaffold material with an agent that produces a known biological effect, the

SEM image of a PET graft coated with a PGS film.

FTIR Image of a PET graft coated with a biologically loaded PGS film.

overall textile product becomes an active participant in healing. Covalent or ionic attachment of growth factors that can be released from the device and into the surrounding tissue in a controlled manner would serve as one such platform for active healing. It is important to employ a system of features that act together rather than limit the device to only one mechanism.

Newer materials, such as poly(glycerol sebacate) (PGS), are in the early stages of commercialization, and early research performed with the material shows it is a suitable candidate for inclusion in

fourth-generation technologies.[4,5] PGS originates from the laboratory of Dr. Robert Langer and his former post-doctoral assistant, Dr. Yadong Wang. From its inception, PGS was designed with all four generations of materials in mind. PGS is a resorbable polyester made by polymerization of sebacic acid and glycerol, and these monomers have known compatibility with the Krebs Cycle of metabolism.[6] Moreover, the degradation products are less acidic than lactic and glycolic acid, and have been shown to produce a lower acute and chronic inflammatory response from polymer resorption.[7]

PGS can have its own diverse physical and chemical properties: Its physical properties can be tailored based on the degree of polymerization and the molar ratio of glycerol to sebacic acid. At low levels of polymerization, PGS takes the form of a hydrophilic gel. Increased reaction time results in a flexible bioelastomer, and as the reaction proceeds, the bioelastomer becomes a thermoset with more hydrophobic character, as illustrated in Figure 1 by the increased contact angle for the thermoset PGS.
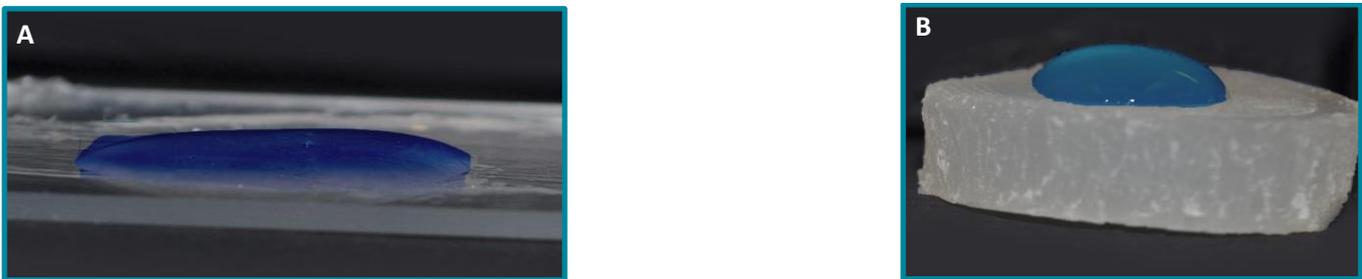

Figure 1.Water contact angle images of PGS with a low (A) and high (B) degree of polymerization.

The change in surface energy is due to the level of free hydroxyl groups, which is specific to the degree of polymerization, and therefore can be controlled by reaction time. In addition to surface energy, the degree of polymerization can be used to control the physical properties of PGS. Figure 2 (p. 7) shows that a range of modulus values can be engineered into PGS by controlling the cure temperatures and that the highest modulus values are obtained at the highest degree of polymerization. Figure 3 (p. 7) shows that the monomer ratio used in the polymerization is a second means to tailor the mechanical properties of PGS in addition to cure time.

An additional benefit of controlling the degree of polymerization is the ability to control the number of available attachment points for the tethering of deliverable compounds. Free acid and hydroxyl groups act as attachment sites for other molecules, which can be useful for crosslinking the polymer or tethering active agents for controlled release. Free functional groups on the backbone are useful for formulating a basecoat from PGS to attach various kinds of active top coats. The active agents should be attached to a PGS coating through either a hydrolytic or enzymatic susceptible bond that can be cleaved over the desired time period to acutely modulate the body's response and enable more effective tissue repair. Aside from growth factors, these agents could be antimicrobials, pharmaceutical ingredients or even components of extracellular matrix that play important roles in wound healing.
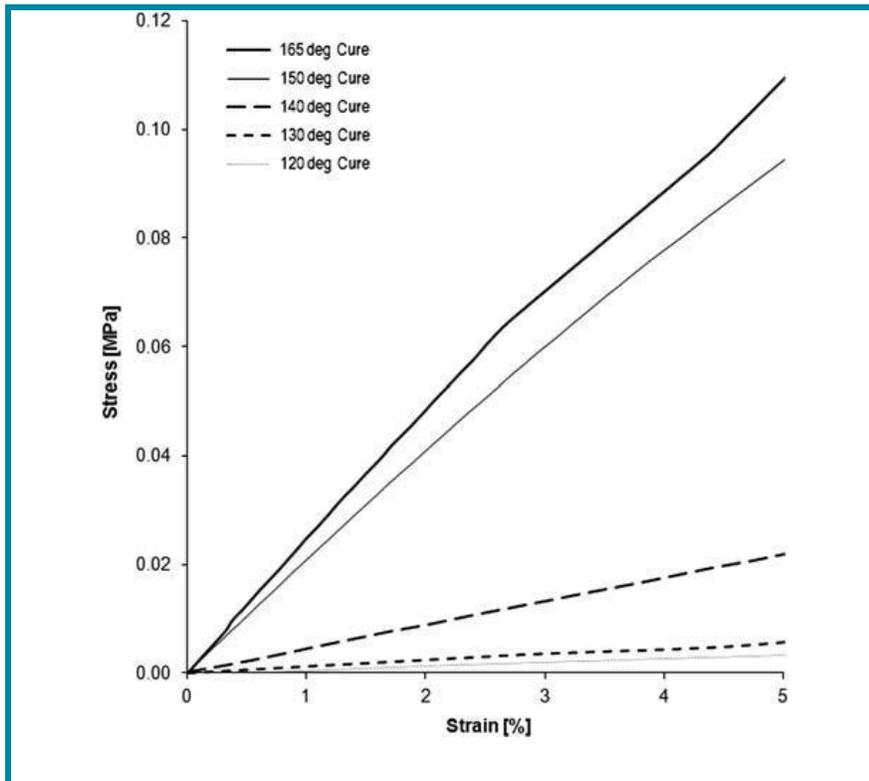
Figure 2. Stress-strain curves for PGS cured at various temperatures.
Image credit: Jaafar, I.H.; et.al. J. Mater. Sci. 2010, 45, 2525.
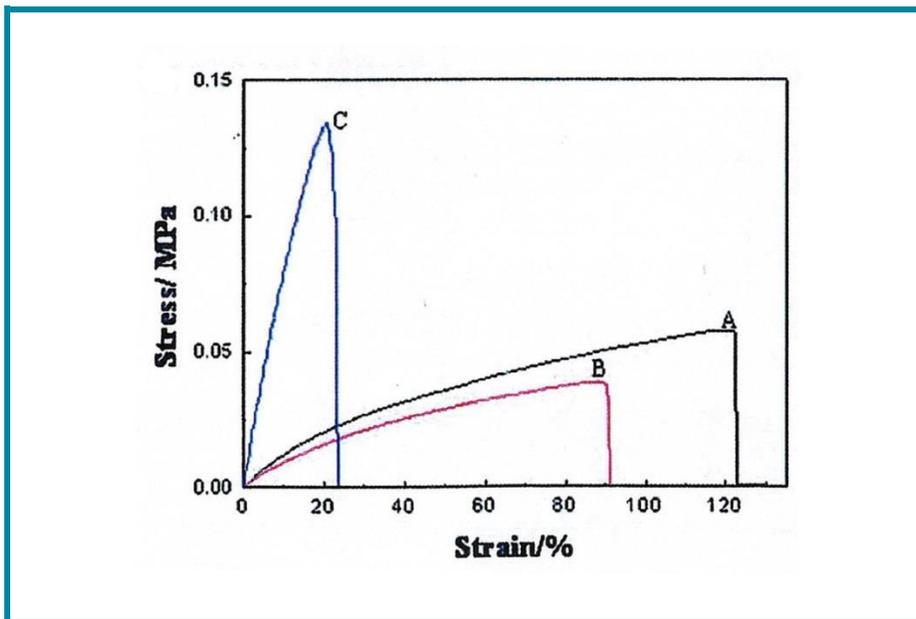

Figure 3. Stress-strain curves for PGS made using varying ratios of glycerol to sebacate: A (1:0.8), B (1:1) C (1:1.2).
Image credit: Sun, Z.-J.; et.al. J. Biomed. Mater. Res. A. 2013, 00A:000-000.

The staggering number of combinations possible as a result of changing the molar ratio and degree of polymerization mean that PGS can be customized for fourth-generation applications. Textile coatings from these combinations are a way to add value to the medical devices they adorn—value that comes in the form of increased capabilities for new and established devices, and a more coherent method for tackling a specific injury or application, such as an upgraded treatment that causes fewer biomaterials-related complications or problems with tissue healing. Picture a coated wound dressing that overcomes the inhibition of wound healing seen in diabetic patients. A device that has already been cleared or approved could be retroactively coated with third-generation regenerative properties without some of the high barriers to entry faced when starting from an entirely new device concept.

Successful Commercialization of New Biomaterials

Many engineers tend to gravitate toward materials that are tried and true. Most resorbable devices on the market are made from some combination of poly lactic acid (PLA), poly glycolic acid (PGA), poly caprolactone (PCL), or poly dioxanone (PDO). While each major biomaterial has its own story, there are three common reasons for the adoption of the major resorbables used today and the lack of adoption of the rest:

1. The majority of the commonly used implantable resorbable biomaterials were first characterized between 1960 and 1990, when FDA regulatory hurdles were lower. Since the materials are established, manufacturers tend to use them to simplify their projects.

2. Much of the device innovation that takes place at the corporate level is stifled by a fear of failure. Paradigms about how the FDA and the European Commission view new biomaterials often kill projects before they even get a shot at regulatory review.

3. Academic institutions that develop new materials often lack an understanding on how to bring their new technologies to market, and they are ill-equipped to deal with the new regulatory landscape.

Regenerez®: Commercializing PGS as a Multigenerational Regenerative Biomaterial

Regenerez is Secant Medical's commercially produced PGS polymer resin. With further modification or processing, the material can take on qualities of one or more generations of biomaterials. In its commercially available form, the material exhibits a low degree of acute immune response upon implantation, and its degradation rate is tunable in conjunction with its hydrophobicity and flexibility. Depending on degree of polymerization, the processed resin can form gels, elastomers and thermosets. These qualities allow the material to effectively perform second-generation tasks, and with applicable engineering, the modified polymer can exhibit bioactive and regenerative capabilities. Regenerez leads the field as an example of a diligently and methodically commercialized biomaterial.

All of these reasons add up to cost, risk and time. Tougher FDA and EU regulations for new biomaterials means that more testing may be required to prove safety and biocompatibility. Earlier generations of materials were not subjected to the same rigor as new materials are today, and since these materials require new data generation, the cost and risk to use a new material may be higher. Despite incurring additional costs, the end result still can be rejected by the regulatory body.
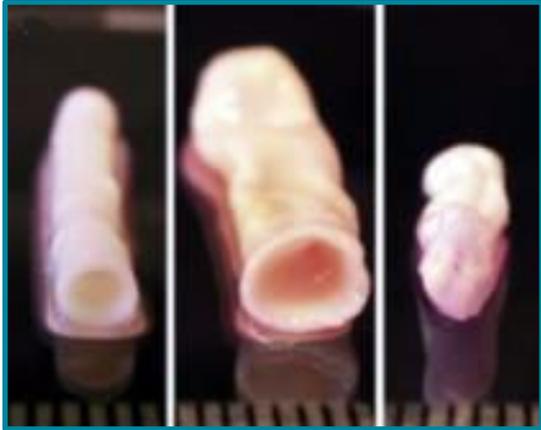
Getting around the hurdles of working with new biomaterials is challenging but not impossible. First, it requires relinquishing the fear of failure. Second, it requires partnership with entities willing to do the leg work of proving safety and biocompatibility for the material alone, so there will be no surprises when it comes time for testing on the final device. The key here may be to separate the device developer from the material developer. Having a separate company invest in proving the material so it can be further used by others farther down the supply chain can spread the cost and risk to an acceptable level for both parties involved. The level of investment by the material development company is smaller than that of the device supplier, which sees the overall device market as the target, whereas the developer is focusing on the biomaterial market. If material development companies or laboratories invest in the early research needed to placate regulatory scrutiny, corporate interests can be more secure in their use of the material.

Although it is conceivable that a university laboratory could perform the necessary work to instill enough confidence in a device manufacturer to use a newly proven material, it requires a slightly different focus. Traditional academic pursuit focuses on a singular quest of new information and ideas. Biomaterial development, on the other hand, requires laborious pursuit of data gathering. New discoveries about the material may or may not happen in this process, but for the most part there is an established list of data points required for every material used in human patients, as well as some extra data that may be unique to a given material. This work may not excite and stimulate an average academician, but it does lead to direct human benefit.

University professors that wish to contribute to this endeavor must move from making novel discoveries to making a usable product (for example, a biomaterial resin). Along with the customary lab work, this also requires cataloging the data into a form usable by regulatory agencies, and packaging the product into a form usable by device manufacturers. However, even at ideal expression of this method, a corporate partner will most likely be needed for distribution, because university environments are poorly suited for this type of marketing and sales work.

The Transition to a Wholly Regenerative Device

How will the healthcare landscape look when biomedical textile components and their devices are wholly regenerative? The use of first- and second-generation materials will diminish, particularly once third- and fourth-generation materials capable of handling the mechanical loads emerge and gain acceptance. The entire structure may be made from fibers drawn from these materials, instead of being coated with a bioactive agent.

Macroscopic appearance of the tunicae media and intima of a porcine carotid artery and a PGS construct.

Image credit: Crapo, P.M.; Wang, Y. Biomaterials 2010, 31, 1626.

Regenerez is one material that will help facilitate regeneration within the body. As a surface-eroding material, its degradation profile can be controlled so the material does not experience a sudden breakdown, as seen with PGA or PLA. When working with bulk-eroding materials such as PGA or PLA, loss of strength occurs as 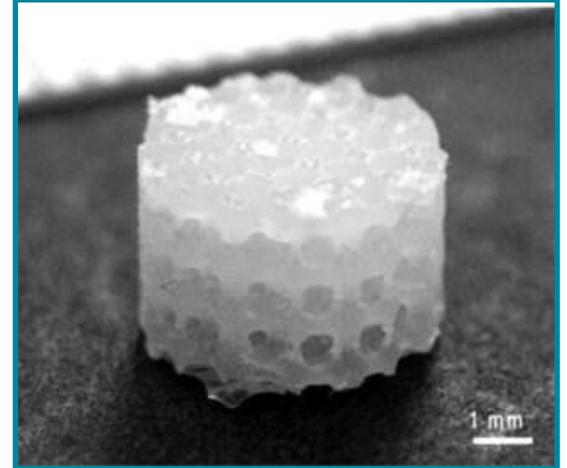water molecules penetrate deeper into the structure. For example, when creating a scaffold with PLA, as the material degrades, the pH can drop too low to elicit cell attachment and natural tissue development. The goal is to control the degradation such that the cell load can be transferred in a manner that does not cause sudden failure of the scaffold. Using a material such as PGS—one that degrades in a predictable manner, does not abruptly lose strength, and has a reduced acid burst—will encourage the body to heal itself without promoting excessive inflammation. PGS has considerable potential in a range of medical device applications, including surgical meshes, heart valves, tendon and ligament repair, and nerve regeneration.

New fibers made from PGS have interesting properties. Core-sheath techniques can be used to form fibers with dual, tri, or quad functionality depending on how many layers are built into the fiber. A multi-layer fiber can have a quickly degrading outer layer designed to address inflammation and an inner layer with a slower degradation profile that contains agents important in the middle and later stages of healing. For bone tissue, this could be an outer layer with a type of PolyAspirin, a polymer created from salicylic acid (the principal metabolite of aspirin), set above an inner layer that contains osteocalcin or another growth factor involved in mid-to-late bone formation. The fiber shape could also be tailored toward cell migration, and its shape could change depending on when and where the cells must migrate. By creating a smooth fiber, some cell types would react by quickly moving and proliferating along the length in a non-directional fashion. At a later point, the fiber would partially resorb to leave a purposely roughened surface that would promote cell differentiation once the cells arrived at the intended location and proliferated. Alternatively, fibers could contain grooves designed to directionally guide certain cell types to different parts of the device. Furthermore, with overall control of the design and porosity of a textile, the mechanical forces within the device could be tailored. Since

mechanical forces are critically important for tissue development, the appropriate types of forces can be applied for the specific application to achieve tissue growth in a three-dimensional space.

Currently adopted biomaterials can address certain health issues acutely. However, fixing problems acutely is not the solution, because it often involves revision surgery and leads to higher healthcare costs in the long run. Multiple new second-generation materials (besides the well-trodden lactide-glycolide permutations) are entering the market each year. Some of these materials are being used in neurosurgical devices like nerve cuffs, and others are in the form of hernia meshes made from tyrosine-derived polyarylates. Other examples abound.

A 3D-designed PGS scaffold for cartilage regeneration.

Image credit: Hollister, S.J.; Kemppainen, J.M. J. Biomed. Mater. Res. 2010, 94A, 9.

The fourth generation of biomedical textile structures is taking shape from a convergence of second-generation material development and bioactive agent exploration. By enabling the creation of structures that improve the long-term chronic response by reducing inflammation, preventing secondary procedures (thereby cutting costs), and enabling the body to regenerate on its own, Regenerez, and this new generation of biomaterials, presents a value proposition that cannot be ignored in today's healthcare environment.

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