White Paper:

Textile Engineered Tissue Scaffolds Offer Advances in Hollow Organ Regenerations

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Regenerative medicine (RM) holds the potential to address some of society's most intractable health problems and restore or establish normal bodily function. Today, regenerative medicine is an emerging technology that relies on the convergence of a number of competencies in biotechnology and bioengineering. By merging these collective competencies, researchers hope to provide the critical answers to the complex problems of tissue engineering and extend these concepts into regenerative medicine.

Advanced high definition 3-D textile architecture (HD3DTA) employed in the creation of luminal scaffold constructs is one example in which regenerative medicine has enjoyed the convergence of strategic technologies and resources. A significant proof point is the pairing of biomedical textile engineering with innovative fiber biomaterials in tissue scaffold development. These luminal structures with 3-D functional mechanical architectures can enable the engineering of hollow-bodied constructs for numerous hollow organ regenerative applications.

Endogenous Recruitment

Innovation has advanced RM. The field of tissue regeneration and reconstruction is based on three major and innovative technologies: (1) stem cell technology, (2) growth factor technology, and (3) biomaterial technology.

Biomaterials have made a significant impact in RM not only through implantable and biodegradable medical textiles, but also in the 3-D architectural and bioengineering approach to organ scaffold design. Advanced biomaterials will eventually transform such traditional textile engineering activities into the next generation of therapeutic applications.

Tissue engineers have faced a number of RM challenges. One of the great puzzles in tissue engineering and regenerative therapies revolves around the persistent belief that eventually biotechnology would discover the switch to turn-on or turn-off the necessary cell processes that would allow the transplantation of healthy *in vitro* cultured tissues. The puzzle lies in the fact that *in vitro* success has never fully translated to *in vivo* success. Now, the prevailing mentality has become to encourage endogenous (*in vivo*) cellular mechanisms to bring about the body's natural self-healing process. This activity is termed "endogenous recruitment."

Progenitor or healing stem cells, specifically destined for the repair and regeneration process, circulate throughout the human bloodstream. Many of these healing stem cells reside quietly, waiting in niches associating with specific organ tissues. Endogenous recruitment requires that the micro- and macro-architectural designs of endogenous tissue scaffolds provide functional mechanical properties for these cells to proliferate in a simulated organ-like matrix. These matrices must experience mechanical properties and native forces associated with the natural molecular and cellular processes within the functional organ system in order to prompt cells to naturally populate the scaffold or to encourage endogenous recruitment of the body's regenerative cells with the help of growth and trophic agents. The engineer merely provides the appropriate stage for this tissue regeneration to play out on.

Impact of Convergent Technologies

Synthetic biomedical textiles have long enjoyed an important role in implantable vascular graft technology. The basic constructs familiar in synthetic textile repair can now be confidently transformed into biodegradable tissue scaffolds by changing the building block materials of construction. The impact of coupling new biomaterials with precision textile engineering allows the tissue engineer the ability to control multiple functional tissue mechanical properties of the biodegradable with "rational, or modifiable, scaffold design. This technology presents a number of innovative approaches to scaffold performance *in situ*. Hollow organ architecture in scaffold design using Secant Medical® high definition 3-D luminal constructs offers a number of applications, among the most obvious being vascular tissue engineered scaffolds.

The vascular scaffold is analogous to the 3-D support matrix-architecture into and onto which organ cells regenerate into the tissues of importance. A key distinction between grafts and scaffolds is that the scaffold is deliberately intended to be a temporary structure and is designed to be resorbed by the body over time as the scaffold is populated by the organ tissue. Resorption supports tissue remodeling. In contrast, vascular grafts are permanent implant devices. In the simplest terms the graft is a foreign body. Unfortunately, with time we have learned that graft implants have limited ability to replicate biology. This limitation is the driving force behind endogenous recruitment. Material advances now allow more reliable bio-inspired structures to be designed to support tissue regeneration.

Intelligent/Compliant Design

The use of FDA-compliant material allows faster commercialization of devices incorporating bio-medical fibers.

Historically, scaffolds have been developed from a number of technologies including non-woven fabric, polymer extrusion and molding, electro-spun extrusion, die-stamping, polymer hydrogel compositions and 3-D printing. Only textile engineering using advanced biodegradable fiber compositions and controlled release design provides the researcher with precision design control. While many of the traditional processes are capable of providing acceptable research structures the researcher must keep in mind that all of these material constructs must be prepared using FDA-compliant materials if the objective is to get to the commercial level.

Unfortunately, this critical compliance fact is systematically disregarded in biomedical research. It is not enough to solve the problem with an engineering process: the materials of composition or construction must all comply with federal regulations or the commercialization of that device will be stalled or ended. An additionally important adjunct to textile engineering is precision structural architecture. Many of the other technologies mentioned above such as electro-spin or non-woven fabric are subject to poor mechanical properties and enormous dimensional instability with small changes in environmental conditions. Here too is the need for precision is critical to regulatory quality requirements.

The attractive feature of biomedical textile engineering is the host of available, FDA-approved synthetic, biodegradable polymers. Selecting fibers or yarns designed from these compliant feed-stocks results in a compliant end product, eliminating the need to modify the extrudates with unregulated processing aids or chemicals during the fiber melt-flow process. The choice of compliant master-batched polymers in biomedical melt-flow textile scaffolds removes the unnecessary burden of separately testing the chemical or polymeric components of the device for safety. This is an intelligent design approach to scaffold building.

Managed Degradation

The custom design of scaffolds using biomedical textile fibers offers critical advantages in managed degradation.

An important design control in scaffold development is to avoid what is known as a scaffold collapse or scaffold crash. Avoiding these malfunctions requires attention during the design process to the simultaneous activities of tissue growth and scaffold degradation. As the organ develops it must penetrate the engineered scaffold and establish tissue mass as it organizes into organ form. In tandem with this tissue growth, the scaffold degrades and diminishes in both material mass and structural integrity. If the scaffold degrades more rapidly than the maturity of the tissue mass, or if the accumulation of tissue mass increases beyond the scaffold's structural integrity, then the scaffold collapses and the tissue growth process fails, not to mention that the engineering effort is lost. In an important innovation, new biodegradable polymer compositions will allow the designer temporal features unavailable just a decade ago. Multi-layer cell-bed constructs with support filament reinforcement can extend exposure periods to provide prolonged stages of scaffold physical stability. And in difficult anatomies, these advanced compositions allow the design of hybrid degradable | non-resorbable structures that can be super-reinforced.

By choosing the appropriate fiber and yarn composition, a design engineer can create a scaffold that manages degradation. Some biodegradable polymers like polyglycolic acid (PGA) degrade quickly; whereas, in contrast, biodegradable polymers like polylactic acid (PLA) have extended resistance to biodegradation. Combining or intermingling yarn stocks in a braided structure made from a combination of PGA and PLA yarns can precisely extend the engineering strength beyond the degradation period of a yarn made entirely of PGA. And likewise, biodegradable polymers can be intentionally customized to create a single copolymer of specific PLA/PGA ratios that further manages the degradation time in a single yarn sample. Additionally, an assortment of engineering properties can be designed-in using other monomers as feed stocks. These important and innovative "precisely managed degradation" design features are difficult if not impossible to achieve with a non-woven structure. The key word here is precisely; that is the success factor is repeatability. These structures when composed of standardized yarn or fiber chemistries define their own quality control.

In addition to the basic polymer composition, advanced fiber technology allows the engineer to design fiber cross-sections with both internal and external architectural features that include

both the physical external geometric features coupled with the potential to spatially incorporate bioactive compounds to be temporally released throughout temporal degradation.

Scaffold Collapse in Non-Wovens

Non-woven scaffolds are particularly susceptible to scaffold collapse for a number of reasons. First, the non-woven process has limited pore size control as a result of the random accumulation of fiber that is compressed into a mat before forming the scaffold structure. This variability in pore size can retard the cellular migration into the bulk structure if the pores are too dense.

Second, even if it were possible to co-extrude two fibers with varying degradation rates into a single non-woven structure, it is difficult to precisely, or repeatedly, compress the mass into a uniform mat. The accumulation of fiber creates a random pattern from the drop-down source. The random accumulation of two dissimilar polymers can influence degradation rates that can lead to pockets of degradation resulting in uneven degradation patterns and unexpected collapse.

Third, the random pattern of the non-woven eliminates any chance of engineering-in either structural strength patterns or anatomic geometries, such as contour guides or circumferential alignment. Here the use of textile engineering technology offers an innovative feature: the textile structure can be designed to not only enhance strength, but to also approximate biomimetic structures. Adding the ability to select the advanced polymer compositions of the fiber or yarns allows the bioengineer the option to design-in controlled release and degradation of the scaffold matrix.

Functional Conversion and Remodeling Enable Recruitment

The aforementioned features are physical advantages of textile structures coupled with chemistries of construction. A biodegradable organized textile scaffold structure offers the tissue engineer another advantage: controlled functionality. For instance, once a scaffold is constructed using textile technology the structure can be chemically post-treated to expose chemical functional groups to which trophic agents can be bound.

A structure having a designed-in specific PGA-based composition can easily convert PGA surface functional ester groups to hydroxyl and carboxylic acid groups by simply exposing the structure to a dilute aqueous solution of potassium hydroxide (KOH). These newly exposed functional groups can be selectively bound with a plurality of bioactive compounds to enhance recruitment. The benefit of this conversion is that yarns and structures can be designed to have sacrificial sites, thus optimizing engineering strength integrity as a result of the surface treatment.

Finally, these textile engineered scaffolds can be remodeled. The basic superstructure of the design can be further modified at the microstructural level with hydrogels, bioactive coatings, spatially resolved droplet deposits, electrospun fiber fine networks, as well as application technologies that will provide gradient custom enhancements of the spatial geometry.

Summary

Biomedical textile engineering affords critical innovations in scaffold design, particularly where structural repeatability, spatial geometry, and engineering strength support the cellular processes in a consistent fashion. These factors illustrate the important impact that the convergence of a traditional installed base of engineering techniques, combined with new materials, offer for successful advances in regenerative medicine.

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