SurFACTS in Biomaterials

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INSIDE THIS ISSUE

From President Angela DiCiccio

Hello and welcome to our 30th year of pioneering the dynamic, forward-looking Surfaces in Biomaterials Foundation. It is an honor to serve as your president this round and I hope that my charter to expand the diversity and cross-functional breadth of our community resonates with your collective objectives. As we embark on this project, I offer an open invitation for feedback, collaboration and contributions by encouraging everyone to reach out and engage as we construct our next adventures.

As we depart from our 2019 season, I'm mindful to reflect on important events from last year that set the structure and trajectory for next year's journey. First and most meaningful is the passing of Lawrence Salvati, our founder and spark that ignited and fostered our Foundation to grow into the prospering community it is today. This year we honor Larry's vision by empowering the roots of his passion for growth of new membership by supporting student involvement through a student award to enable participation in our annual workshop, funded by donations to the Lawrence Salvati Jr Fund. Additionally, the 2020 Workshop and Symposium will enhance student participation by expanding the poster contest to include opportunities for more public speaking and directed career preparation.

Reflecting on our 2019 workshop and symposium in Park City, Utah, I want to extend a huge thank you from the entire community to our past-president Rob Kellar and the outgoing board and committee members for their thoughtful and thorough dedication to crafting an inspiring workshop diving into Implantable Sensors and an exciting symposium including a heated debate over implanted vs. non-implanted sensors. Some highlighted sessions include an energetic afternoon by our fantastic keynote speaker Ali Khademhosseini, who spoke about transforming the application of hydrogels in regenerative engineering to enable advanced control over the growth of new biointerfaces. To complement, our Excellence in Biomaterials Award recipient

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In memory of Lawrence Salvati Jr., Surfaces in Biomaterials Foundation Founder

On September 3, 2019, Larry Salvati Jr., founder of the Surfaces of Biomaterials Foundation, passed away en route to the BioInterface 2019 Workshop and Symposium. He often referred to the Foundation as his “greatest and most rewarding scientific achievement.” Larry loved bringing people together to share ideas and solve problems. For the past 30 years, the Foundation has flourished around the ideal that technical challenges can be solved by fostering education and multidisciplinary cooperation among industrial, academic, clinical and regulatory communities. Larry was inclusive to all ideas brought forth in our community. He also encouraged students to pursue their passions and to establish a diverse set of scientific peers to consul and advise them throughout their careers.

Larry received both his B.S. in chemistry and Ph.D in analytical chemistry from the University of Pittsburgh and always advised engineers to think like chemists. An expert in his field, Larry spent the first part of his career in the R&D labs before moving to management and consulting. He was a published scientist and patent holder. Larry’s obituary can be found here.

To continue to recognize Larry’s impact, the Board voted to establish the Larry Salvati's Remembrance Fund as an annual student award selected based on a statement drafted by the student exemplifying his or her commitment and contributions to advancing the Surfaces field. The award will be presented at our annual BioInterface Symposium.

Donations to the fund can be made at the Surfaces website or mailed to

Surfaces in Biomaterials Foundation
5329 Fayette Avenue
Madison, WI 53713

Excellence in Biomaterials Science Award Winner — Professor Rena Bizios

Nominated by Nicholas Peppas

Professor Rena Bizios of the University of Texas at San Antonio has been recognized with the 2019 Excellence in Biomaterials Science Award. Bizios is one of the most influential and pioneering scientists in the biomedical materials field, and one of the true leaders and visionaries of modern materials, biomedical sciences and engineering. At the same time she is a recognized as the leader in education and mentoring, and her leadership has reached much beyond her present and past universities.

Bizios is a leading authority on biomaterials and cellular engineering. She has made exceptional contributions on materials designed to control, modulate and direct various select, desired, and timely cellular/molecular responses at the tissue/implant interface. She has made pioneering contributions on the modification of material surfaces with immobilized, bioactive compounds (such as select adhesive peptides), on micropatterning of material surfaces in order to direct and control subsequent adhesion of specific cell lines in designated domains, and on novel material formulations (specifically, nanoceramics and nanocomposites) with unique biocompatibility and/or improved mechanical and electrical properties. She has developed new cellular techniques to evaluate the cytocompatibility of these constructs and to determine the conditions needed to promote tissue growth on these materials.

Bizios has been one of the true pioneers in the bioengineering field and has mentored hundreds of students at the undergraduate and graduate level. She has been very active in AIMBE, BMES, SFB and AIChE. She has been the role model of women who wish to pursue bioengineering work as it can be shown from the numerous awards for leadership and the testimonies of students and professors. Indicative of Bizios’s great contributions is that in 2016 she was elected to the National Academy of Medicine while in 2017 she was elected to the Texas Academy of Medicine, Engineering and Science. Also, she received the highest recognition of the Society for Biomaterials, the Founders Award, and the Theo Pilkington Award for Biomedical educator from ASEE.

Measurement of Particulates in Hydrophilic Coatings

Bob Hergenrother, Ph.D., Senior Director, Research & Development, Biocoat, Inc.

Introduction

Hydrophilic coatings for medical devices provide multiple benefits. The coatings can improve the ease of access of a device to the targeted therapeutic site. This enhanced ease of access can even allow improved device functionality by enabling clinicians to go further distal in the vascular anatomy. The lubricious nature of the coatings can minimize vessel trauma as the devices track through the vasculature. All these features have the potential to shorten procedure times, with benefits to both patients and medical personnel. The measurement and testing of hydrophilic coatings for medical devices can be challenging, as they can be tough to see (coatings are typically clear or transparent), most coatings are not activated until hydration begins, and if the coating isn't durable, particles may be left in the body.

Requirements for Lubricious Surfaces

During the development cycle for a medical device, the lubricious coating should have each of the following components:

- Low friction: To ease the movement of the device through the body
- High durability: Due to the many twists and turns the body contains, the coating needs to maintain the same level of performance throughout the entire procedure
- Low particulates: A relatively new measure of coating performance that is driven by various regulatory agencies to understand what types of foreign materials are being introduced to the body and what their long-term impacts on the patient are

How to Evaluate Lubricity

There are two tests typically used for the evaluation of lubricity: pad tests and tortuous path tests.

Tortuous Path Test: A tortuous path test uses a simulation model of the body anatomy of interest. The materials are inserted into the model and they are tested for ease of insertion and to determine flexibility. The test is often run through multiple cycles to determine the coating's durability. This test is also used to confirm that the entire device functions as expected prior to use in potential trial situations.

Pad Testing: To complete a pad test, two matching rubber pads are set at a predetermined width. The material is then inserted between the pads, a predetermined tension amount is applied, and the object is pulled through the pads to measure the force that it takes to remove the materials. A good lubricious coating should offer a minimum of a 90% reduction in pulling force, while a best-in-class coating can offer up to a 95% reduction in pulling force. The pad test is often used when comparing a similar substrate material with different coatings. This allows for a side-by-side comparison of the coatings in question.

Evaluating Particulates

Over the past several years there has been interest from various regulatory agencies about test results and justification for levels of particulates used in coated medical devices. Particulate levels in procedures are influenced not just by the coatings, but also device design, ancillary devices used such as sheaths and guidewires, as well as wipes, gowns and drapes in the operating room. There are several factors that must be considered prior to testing, and each of these factors can affect the particulate counts. At this time there are standards and guidance documents for coatings, but none of these are entirely applicable for the particulates generated from the medical device.

The Current Guidelines Include:

United States Pharmacopeia (USP) 788 – Particulates for Injectable Solutions:

- Defines limits per container for particles in solution >10 µm and > 25µm.
- Provides instructions for counting particles; however, there is no

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President's letter

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Rena Bizios empowered us with insights to the foundations of the tissue-implant surface interactions, reigniting the principles used to understand the formations of these new biointerfaces.

Next year we will continue exploring new cities as we set up for Biointerface 2020 in Portland, Oregon. We are excited to collaborate with the Oregon Health and Science University and hope to see you there!

Warm regards,
Angela DiCiccio

Measurement of Particulates ...

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guidance on how to generate a sample from a medical device or what would be an acceptable threshold.

US Food and Drug Association (FDA) has issued two guidance documents (1. Coronary, Peripheral, and Neurovascular Guidewires – Performance Tests and Recommended Labeling: Draft Guidance for Industry and Food and Drug Administration Staff, June 15, 2018 and 2. Class II Special Controls Guidance Document for Certain Percutaneous Transluminal Coronary Angioplasty (PTCA) Catheters, Guidance for Industry and FDA Staff, September 8, 2010) on PTCA Catheters and Guidewires:

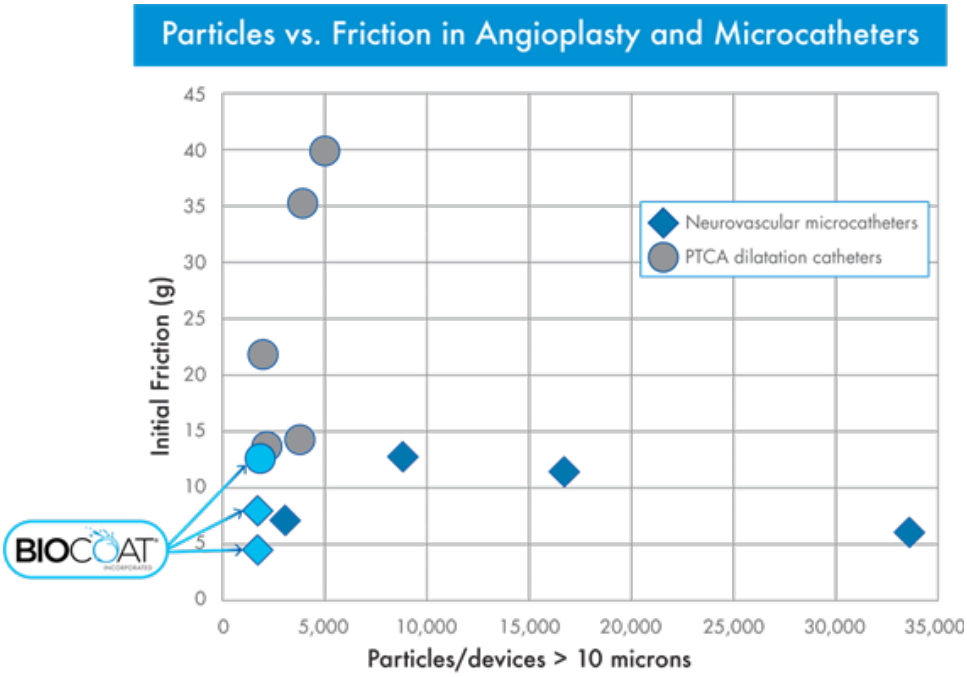
- Recommends counting three sizes: >10, >25, >50 µm using an appropriate simulated use model.

- Recommends providing an interpretation of particulate data but provides no acceptance criteria.

Keys to Particulate | Measurement

The keys to particulate measurement are severalfold. The FDA recommends the use of a simulated model, and one that is clinically relevant. For example, ASTM has a model (ASTM F2394) that is useful for stent retention, and in cardiovascular devices, one could test using this model to track the device's progress through the system and then collect the flush solution after the test completion. For peripheral models one might use something more winding that best represents the tortuous path. Ideally, one would define what the model is and why it is clinically relevant for the device and coating.

Another key to a successful measurement is to define the entire test procedure. There are several ways that one could influence the measurement results.



Some examples include:

- Duration of test and measurement time

- Storage conditions

- Materials of sample containers

- Flush solution

- Particle detection method such as light obscuration or impedance

Whichever test is completed, one should still run comparator and control samples to provide some context for what the value means in interpretation.

In this chart, the Biocoat R&D team tested several angioplasty catheters and neurovascular microcatheters to evaluate lubricious performance and particulate generation. Friction testing was done with a vertical pinch test by applying 470 grams through silicone rubber pads. Particulate evaluation was performed by cycling the catheters through a tortuous path 50 times and flushing with deionized water every 10 cycles. Particles were counted by size and cumulative particles greater than 10 microns are shown above.

There are three regimes that are demonstrated on the graph. High particulate, low friction, typical of several neurovascular catheters. Low particulates, higher friction, typical of several angioplasty catheters. Finally, there is a low particulate, low friction group characteristic of the high-performance coatings.

Our testing showed a broad range of results from commercially available microcatheters and angioplasty catheters. This demonstrates the need to have a comprehensive and consistent evaluation of lubricity, durability and particulate generation and the need to consider the interplay between all three aspects of hydrophilic coating performance.

In Vivo Cell Responses to Porous Polymer-Coated and Bare Metal Coils for Aneurysm Occlusion

Herting, S. (1), Dai, D. (2), Ding, Y.H. (2), Jessen, S.L. (4), Khashim, Z. (2), Nash, L.D. (3), Barry, T. (1), Friedemann, M.C. (4), Clubb, F.J. (1,4), Kallmes, D.F. (2), Kadirvel, R. (2), and Maitland, D.J. (1,3)

1. Department of Biomedical Engineering, Texas A&M University, College Station, TX; 2. Department of Radiology, Mayo Clinic, Rochester, MN; 3. Shape Memory Medical, Santa Clara, CA; 4. Department of Veterinary Pathobiology, Texas A&M University, College Station, TX

An intracranial aneurysm can occur when a blood vessel wall becomes weakened or experiences abnormal stresses, and if ruptured, leads to subarachnoid hemorrhage with devastating or deadly consequences. Platinum microcoils are commonly used to enable endovascular occlusion of these aneurysms to reduce the risk of rupture. However, this treatment fails in >20% of cases due to insufficient occlusion and a lack of tissue remodeling that can stabilize the occlusion.[1] The desired biological response would induce dense collagen deposition within the aneurysm dome to reinforce the coil mass and robust neoendothelial formation at the aneurysm neck to provide a barrier to flow.[2]

Our lab has designed a shape memory polymer (SMP) foam-coated coil device, which is being commercialized by Shape Memory Medical under the name "TrelliX," intended to increase the occlusion of aneurysms and encourage a beneficial healing response.[3,4] Preliminary studies using this SMP foam in porcine aneurysms have demonstrated rapid clotting in the aneurysm dome and a robust healing response as described above.[5,6] We hypothesize that the porous structure of this foam acts as a scaffold for the connective tissue deposition and neoendothelial formation. It has been observed that porous biomaterials can induce beneficial healing responses by affecting the phenotype of immune cells in the foreign body response.[7] Macrophages in particular can be present in a spectrum of phenotypes ranging from the pro-inflammatory M1-like macrophage to the anti-inflammatory, pro-healing M2-like macrophage. The macrophage phenotypes present can influence the level of reactive oxygen species production, the types of cytokines released, and the deposition or remodeling of the tissue.

In this study, we evaluated aneurysm healing 30, 90, or 180 days after treatment with the TrelliX device compared to standard bare platinum coil (BPC) controls in the rabbit elastase aneurysm model.[8] Collagen deposition and overall aneurysm healing were evaluated independently by two pathologists using two published scoring systems. Pathologists also evaluated the levels of inflammation and counted all inflammatory cells present in the tissue. Immunofluorescent staining was used to identify subtypes of macrophages present.

Results indicate that the majority of inflammatory cells present are macrophages, with similar numbers of inflammatory cells observed in each treatment group. Connective tissue remodeling is increased by treatment with TrelliX after 90 and 180 days, and overall healing appears more complete at earlier timepoints. Neointimal tissue thickness was greatest in aneurysms treated with TrelliX at all timepoints. Preliminary immunostaining indicates a skew toward an M2-like response at all timepoints tested. We also observed a more robust M2-like response in aneurysms treated with TrelliX compared to BPCs at the later timepoints.

This work demonstrated the clinical potential of TrelliX as an aneurysm occlusion device that utilizes SMP foam to enhance occlusion and healing. In the future, we will continue to investigate the mechanisms of aneurysm healing, and the role of macrophage polarization in the foreign body response to porous polymeric devices.

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My Poster and Experience at Biointerface 2019

Nicholas Norris, Northern Arizona University

In vitro modeling is used to test and validate medical devices for development and often used as practice for surgeons training on a new device such as a stent or innovative coil. These models are often made of silicone or glass, but these materials fall short on mimicking the mechanical properties of human vascular tissue. These limitations restrict the amount of information that can be drawn from these kinds of materials. My summer research was spent spearheading research on an innovative UV-Cured 3D printed Acrylic polymer that I started calling VC-A30, as it is a mixture of two materials by Stratasys called VeroClear® and Agilus30®. This material can vary in durometer hardness depending on the mixture of the two materials and my team, lead by Dr. Timothy Becker, tested human donor tissue against VC-A30 (30 shore A hardness printed at 1.2mm thickness), VC-A30 (40 shore A hardness printed at 1.2mm thickness), and silicone (cast at 1.8mm thickness). Silicone is a hydrophobic material; however, the VC-A30 reacts when it is bathed for a period of time. This provided an additional mean of tuning this material's properties. The polymers were soaked in a phosphate buffered saline (PBS) and all tests were replicated for bathed materials as well.

Furthermore, the polymers underwent eight tests in order to acquire different modulus of the polymers, Poisson's ratios of the polymers, compliances of the materials and more. These tests were replicated for human donor samples as well and the data was compared. Seven of the tests were preformed using a Discovery HR-2 Rheometer (TA Instruments – **Fig 1-Left**, for Tests 1-7) and a BV Pulsera C-Arm fluoroscope (Philips – **Fig 2-Right**, for Test 8).

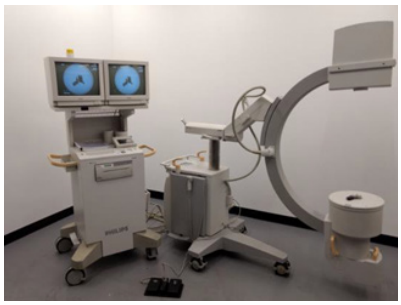

Figure 2. BV Pulsera C-Arm fluoroscope

Figure 1. Discovery HR-2 Rheometer

The tests performed are listed below:

• Test 1: Compressive – Dynamic modulus from 0.1 to 3.0 Hz. Disk samples were used for this test and they were 8mm in diameter. The samples were preloaded, and a 1% strain was used. (Fig 3)

• Test 2: Shear– This test also used preloaded disk samples with a 1% strain. Modulus measured under torsion from 0.1 to 3.0 Hz. (Fig 3)

Test 3: Tensile– Dynamic modulus from 0.1 to 3.0 Hz. Strip samples were used for this test. Samples were measured to get cross sectional areas so that physiologically relevant preload forces could be computed. (Fig 4)

• Test 4: Poisson's Ratio – Diameter change with respect to vertical compression was measured using the optics plate of the DH-2 Rheometer (Fig 5).

• Test 5: Hardness – Vertical force was applied to vessel wall and polymer samples using a 5mm ball indenter attached to the rheometer head (Fig 6).

• Test 6: Radial Force – Force was applied to compress the vessel radially, the same was done to vessel analogs of each material (Fig 7). Diameter changes were recorded with the optics plate while force was measured from the rheometer.

• Test 8: Compliance – radial and axial (% volume) sample change with pressure (Fig 8). Images and measurements taken using a C-Arm fluoroscope. Pressure was introduced using a syringe

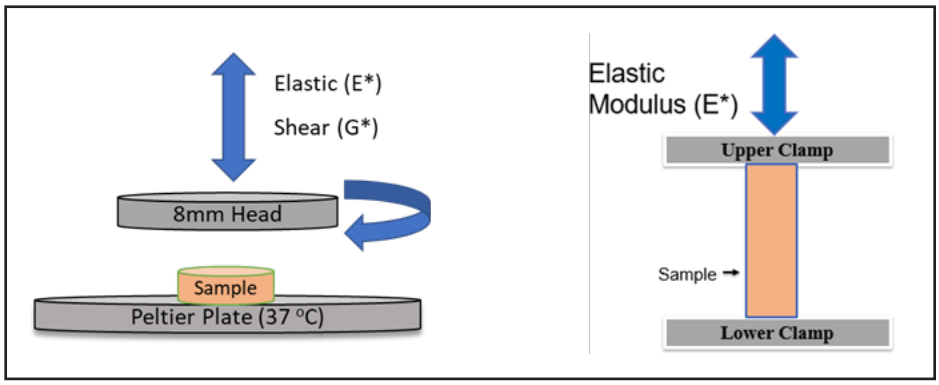

Figure 3. Diagram of Tests 1 and 2

Figure 4. Diagram for Test 3

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My Poster and Experience ...

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filled with radiopaque liquid. The vessel analogs were also filled with radiopaque liquid.

The data was then analyzed and presented at the Biointerface 2019 conference. Overall the data showed that there is currently not a confident model that mimics the material properties of human vascular tissue. The key take-away was that there are now tunable materials that can take on different mechanical properties by making small alteration to the material or prepping it in some way. As technology moves forward, we should be asking ourselves where these innovations can be incorporated in order to advance other scientific communities. It is now known that materials such as VC-A30 can be 3D printed in order to create near exact geometries and even patient specific geometries; moreover, they can be tuned so that their mechanical properties approach human vascular tissue values. With a more confident in-vitro models it may be possible to reduce the amount of costly animal studies that occupy a gray area in science.

The conference allowed myself and my lab mates to practice our presentation skills and I was able to convey this idea of tunable materials to scientific minds that asked me challenging questions. It was an incredible experience that solidified my research in a setting of interest.

Often, students present to other uninterested students. This kind of practice is inferior to the practice I was given the opportunity to take part in. I was given an audience that not only wanted to hear what I had to say but would communicate with me about it and often teach me what they knew and add that information to my own. My research was important and going to conferences allowed me to realize that fact and convey it to interested groups. Many of these groups were looking for engineers to join their team and I was given the opportunity to potentially find a career in a field of my interest as well. The conference was one of the best weeks of my summer and fall semesters combined. It was truly inspiring to go to a conference like this and I would do it all over again in a heartbeat. It might not be a huge impact, but it is awesome to be able to say that I have already made an impact with my degree and with my studies.

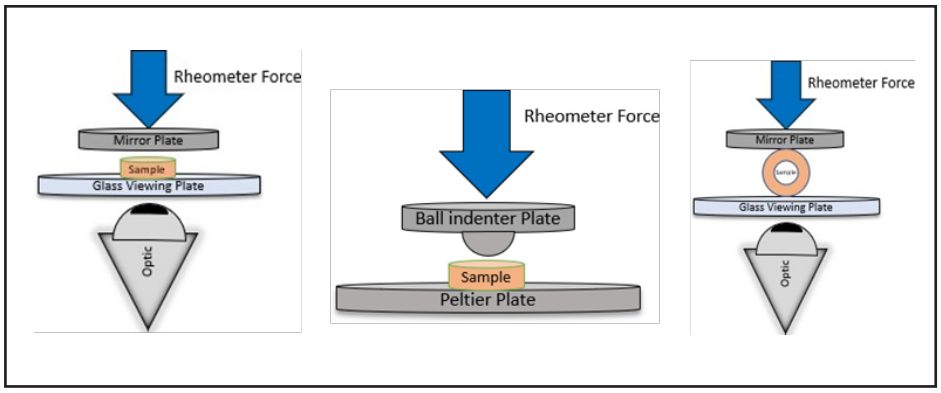

Figure 5. Diagram for Test 4 *Figure 6. Diagram for Test 5* *Figure 7. Diagram for Test 6*

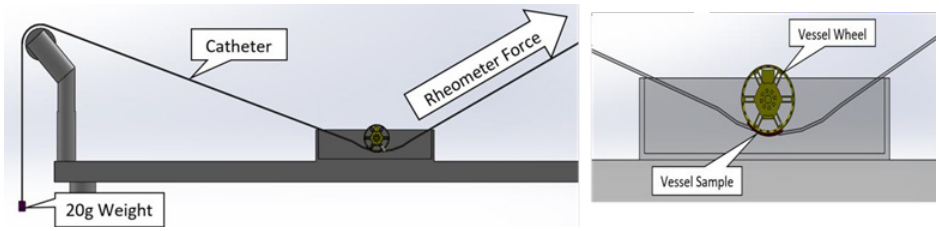

Figure 8. Diagram of Lubricity Test

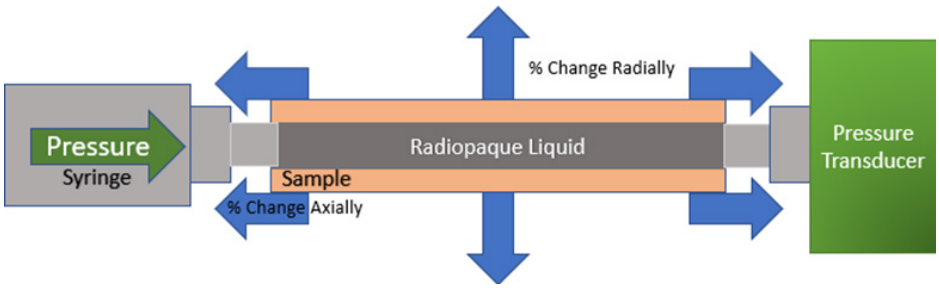

Figure 9. Diagram of Compliance Test

Acknowledgments

Thank you to Dr. Timothy Becker for making this all possible. Thanks to Chris Settanni, William Merritt, Isaac Smith, and April Huckleberry for all your help and support. I could not have asked for a better group to spend my research time with.

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Vascudyne – U of MN Startup Commercializing Engineered Tissue Technology for Implantable Devices

Celeste Blum

From small diameter vascular grafts to transcatheter heart valves, Vascudyne, an engineered tissue startup company based in Stillwater, Minnesota, ushers in a new generation of biomaterials boasting unrivaled regenerative capacity unavailable until now. The startup hopes to lead the charge in helping pave regulatory pathways and push the boundaries of current industry standards to further progress the field of regenerative medicine for both Vascudyne products and other regenerating device companies. It is the company's position that regenerative medical devices are the future, offering solutions where the current standard of care falls short.

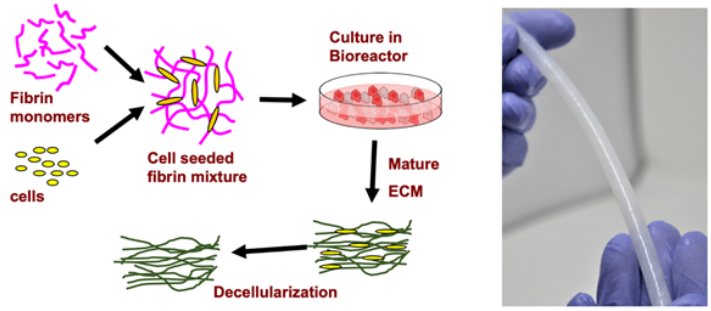


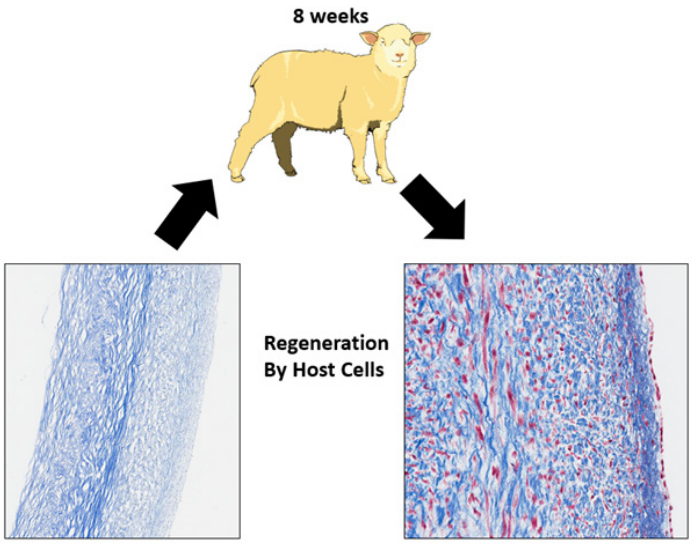
Figure 1: Schematic of development process for engineered tissue in bioreactor from human cells in biopolymer and Vascudyne engineered tissue based small diameter bypass graft

Based on 20 years of extensive academic research and development at the University of Minnesota led by Professor Robert Tranquillo and Dr. Zeeshan Syedain, Vascudyne engineered tissue is formed from human dermal fibroblasts in biopolymer fibrin gel, ultimately yielding decellularized collagenase tissue constructs. "Vascudyne's platform tissue is engineered specific to each device type, allowing us to hone in on key structural and biological features that increase its ability to function in a specific device, whether that be in a heart valve, coating a stent, or in a vascular graft," said Allie Haarstad, a biomedical engineer overseeing Vascudyne's manufacturing process. The current focus is on small diameter vascular grafts and heart valves, but the company intendeds to expand into other areas such as venous valves and tissue covered stents.

The novelty of this tissue-based technology partially resides in its production with human skin cells, whereby the extracellular matrix that resides in the product will not illicit an immune response in a human host. In addition, at the end of the manufacturing process, the tissue is decellularized to remove cells or DNA debris that may cause an immune response. This lack of immunogenicity allows native/host cells to infiltrate the graft and regenerate the tissue over time. Previously, University of Minnesota studies have shown the tissue's ability to completely recellularize and grow in conjunction with host tissue (1-7). In a study by Syedain et al, the pulmonary artery in a growing lamb model was replaced with the engineered tissue graft. Over the duration of 1 year of implant, the engineered graft demonstrated somatic growth in animals demonstrating the engineered tissue technology's value for pediatric cardiovascular applications. This capacity to remodel and anatomically grow with patient could eliminate the need for multiple surgeries in a child with congenital cardiovascular defects (8).

Other key in vivo facets of Vascudyne's technology, aside from a lack of immune response and regeneration into host tissue, include a lack of calcification as demonstrated in the highly calcific

lamb model (1) and meeting/exceeding the required strengths on an individual device basis. Vascudyne's tissue has achieved tissue strengths (burst strength >4000mmHg) that match or exceed native tissues (human internal mammary artery 3196 ± 1264mmHg) and has similar mechanical properties (suture retention > 300 gram-force) to that of glutaraldehyde fixed pericardium (the current industry standard for heart valve tissue). An



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Exogenesis Corporation Receives Regulatory Clearance for Its First Device with Nano-Modified Surface

Joseph Khoury, Ph.D., Vice President, Biomedical, Exogenesis Corporation

Exogenesis Corporation, a nanotechnology company commercializing its Accelerated Neutral Atom Beam (ANAB) technology, recently announced that it has received clearance from the US Food and Drug Administration (FDA) for its first proprietary soft tissue repair device, Exogenesis Hernia Mesh. This represents the first surgical mesh that is surface modified at the nanoscale. Dmitry Shashkov, President and CEO of Exogenesis commented, "We are thrilled to receive FDA clearance of the Exogenesis Hernia Mesh premarket application. We are currently completing commercial channel development for this novel product and look forward to bringing it to the clinical community in the near future."

Exogenesis' core platform technology, Accelerated Neutral Atom Beam (ANAB), is a low-energy particle beam that was developed for ultra-shallow surface modification, modifying material surfaces at depths of 1-3 nm. Processing materials with ANAB results in a physical modification without adding any atoms in the surface, thus it is not a coating. Joseph Khoury, Ph.D., VP of Biomedical at Exogenesis noted, "Since the outer surface of an implantable material is the only part that contacts bodily fluids and cells, it is advantageous to treat only the shallowest depths possible. As the bulk of the material does not get modified, and since nothing is added to the surface, this allows for an easier regulatory pathway."

Seen more in depths, ANAB is a related but a distinct technique that has evolved from the Gas Cluster Ion Beam technology (GCIB). GCIB has many applications in the semiconductor and optics fields as well as in material characterization such as SIMS and Auger Spectroscopy equipment. To create ANAB, a stream of argon (Ar) clusters is formed via adiabatic expansion of pressurized gas into vacuum through a specially shaped nozzle. Clusters of 500-5,000 atoms (approximately spherical in shape, 1-4 nm diameter) are formed, bound by van der Waals forces. The clusters are then ionized by electron impact ionization and accelerated to energies from 20-50 kV. Cluster dissociation is then promoted by orchestrating cluster collisions with slow-moving gas molecules present along the flight path. Finally, all charged species are removed from the beam by an electrostatic deflector. With ANAB, the dissociated clusters form "clouds" of individual gas atoms or molecules traveling near each other with essentially the same speed and direction and arriving nearly simultaneously to the target surface. ANAB technology can impart beneficial functionality on metal, ceramic, glass, and polymer surfaces without detrimental impacts of traditional surface modification techniques such as plasma and ion beam technologies. ANAB provides an intense, collimated beam of neutral gas atoms with highly controlled energies from 10-100eV per atom, an ideal range for many nanoscale surface modifications. This non-additive technology results in modifications of surface topography, structure, and energy.

The global hernia repair market is forecasted to reach $5.3B by 2023 ($1.3B in the US). Hernias often occur at the abdominal wall and are generally visible as an external bulge especially during straining or bearing down. It affects people to a large extent, causing significant pain and discomfort. Age, pregnancy, obesity, muscle strain, and surgery increase the risk of hernias. Surgical meshes of various construction have been in use since late 19th century. In recent years, research in the area has increased due to increasing numbers of post-surgery complications such as infection, fibrosis, adhesions, mesh rejection, and hernia recurrence. Research has focused on the analysis and implementation of a wide range of materials and coatings; meshes with different fiber thickness and porosity, a variety of manufacturing methods, as well as surgical and implantation procedures. Most recently, surface

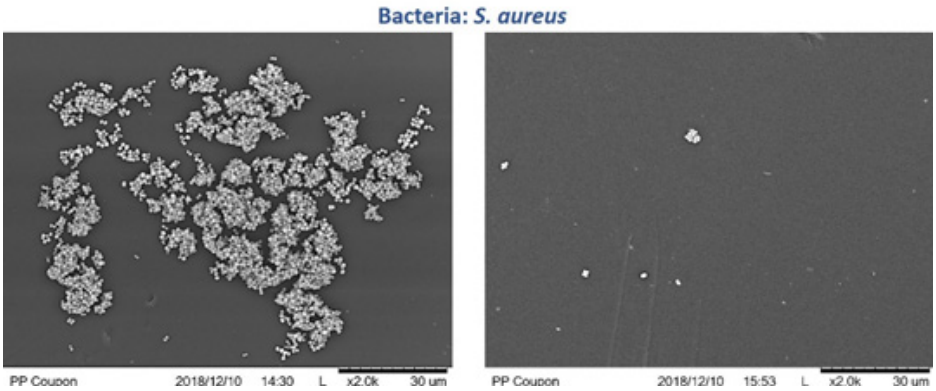

Figure 1.* S. aureus *attachment on polypropylene coupons, 4-hour timepoint; Control (left) vs ANAB-treated surface (right)

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Vascudyne ...

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arteriovenous graft study performed at the University of Minnesota in a non-human primate model demonstrated the lack of immune response. Additionally, 6 months of implant including access with dialysis needle proved robust mechanical properties of the product including puncture wound site healing (6).

As a platform technology, the engineered tissue manufactured by Vascudyne could be used for a plethora of devices offering benefits that current standard of care devices cannot meet. To learn more about Vascudyne and their tissue engineered products, visit www.vascudyne.com.

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Exogenesis Corporation ...

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modification methods as well as the development of nanofiber-based systems are actively being explored as promising pathways to increase biocompatibility of available mesh.

In vitro data on ANAB-treated polypropylene shows significantly enhanced fibroblast attachment and proliferation, suggesting better tissue integration in vivo. Perhaps even more importantly, Exogenesis has also demonstrated a reduction in bacterial attachment on ANAB-treated coupons as compared to untreated controls. Figure 1 shows the difference in the ability of *S.aureus* to attach on control versus ANAB-treated polypropylene coupons. This could represent an advancement in the current materials used for surgical mesh to combat potential surgical site infections.

Exogenesis Hernia Mesh is constructed of monofilament medical grade polypropylene and surface treated with ANAB technology. It is the first hernia repair device in the market with surface nano-modification. The Exogenesis Hernia Mesh is indicated for the repair of abdominal wall hernia defects, including inguinal (direct & indirect). The Exogenesis Hernia Mesh is not indicated for transvaginal pelvic organ prolapse repair.

Members are encouraged to submit articles for future editions of SurFACTS. Please email your report (with all appropriate figures and graphics) to Newsletter Committee Chair Melissa Reynolds at melissa.reynolds@colostate.edu *for consideration in a future issue. Deadlines for upcoming issues are posted on* surfaces.org.

Tissue Engineering for a Better Tomorrow

Jed Johnson, Nanofiber Solutions

Introduction

Re-growing limbs, organs, and recovering from irrevocable physical losses is no longer just for science fiction characters or the next Marvel Comics movie due to the advancements being made in regenerative medicine and tissue engineering. Regenerative medicine is the process of creating functional tissues to replace tissues or organs that have been damaged by disease, trauma or congenital issues and to create solutions for organs that have become permanently damaged. The terms regenerative medicine and tissues engineering have become interchangeable; however, tissue engineering is a concentration or subfield of regenerative medicine. The focus of tissue engineering is to create constructs that restore, maintain, or improve damaged tissue or whole organs through the process of combining scaffolds, cells, and biologically active molecules into functional tissue [1, 2].

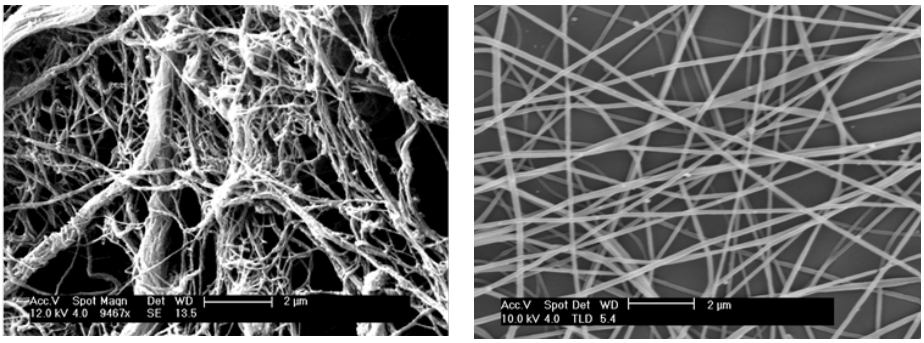

Figure 1. Scanning electron microscope image of Left: a decellurized blood vessel demonstrating the fibrous structure found in human tissue, Right: a synthetic nanofiber scaffold.

According to Stratistics Market Research Consulting, the Global Tissue Engineering market is expected to reach $16.82 billion by 2023[3]. Three different areas categorize the tissue engineering market: synthetic, biological, and genetically engineered solutions. Generally, the synthetic products currently available (e.g., polypropylene hernia meshes) can be manufactured on a large scale but do not provide the environment required for the cells inside the body to properly grow into and integrate in the mesh, resulting in severe scar formation. The biological solutions (i.e., allografts) can be integrated into the body, but suffer from problems with variable outcomes such as premature degradation and immune system reactions, sourcing of materials, and high cost [4]. The genetically engineered solutions typically consist of cells being grown in a bioreactor in the lab to create a functional organ that can be implanted, but this is hugely expensive and still in early development. ParaGen Technologies aims to redefine tissue engineering with the development of a new type of synthetic scaffold capable of rapid biointegration, highly reproducible patient outcomes, no immune rejection, and high function regrowth. The core technology of ParaGen Technologies is the synthetic nanofiber scaffold from Nanofiber Solutions that mimics physical structures (Figure 1) found within the body and allows for assimilation and tissue level structural support. The nanofiber scaffold is made from completely synthetic polymers (e.g., the same polymers used in resorbable sutures such as polyglycolide (PGA)) and resorbs overtime so no foreign material remains in the body.

Background

The fields of tissue engineering and regenerative medicine as applied today are relatively new; only about twenty years old. As the times change and the needs of healthcare providers shift, so does the focus and research of regenerative medicine. From the 1900's to the 2000's there was a change of focus in regenerative medicine; from symptomatic treatment to curative treatment [5, 6]. According to Allied Market Research, the global regenerative medicine market is expected to reach $67.5 billion by 2020. The high-cost pressure on healthcare providers due to an aging population and the increasing prevalence of chronic diseases is what continues to drive interest in tissue engineering and regenerative medicine despite the early setbacks and what some would consider as lack of significant progress [2, 5-7]. While the Department of Defense (DoD) is one of the largest funders of regenerative medicine research, their focus is on limb repair and battle field injuries, but tissue engineering has the potential to fix both traumatic injuries and chronic diseases. According to the Centers for Disease Control and Prevention, out of the top 10 causes of death in 2014, seven were in connection to chronic diseases. It is the possibility of addressing cardiovascular disease, neurological conditions or chronic diseases, the potential to repair, replace or regenerate damaged organs and tissues, and the limitations of suitable organs for transplantation that continues to push the field of regenerative medicine and tissue engineering forward [8].

How does regenerative medicine work? The repair principles of regenerative medicine are rejuvenation, regeneration, and replacement [5, 7]. In simple terms, the process begins with building a scaffold that allows

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the body to repair itself just like the scaffold around a building allows the workers to repair the structure. Once a functional scaffold is created, cells can be added, and tissue will develop with the scaffold if the environment is right. Tissue engineering has three main components; cells, scaffolds, and biochemical signaling [1, 9, 10]. In this approach, cells are seeded on a polymeric scaffold that is then transplanted into damaged areas to repair them. In this traditional tissue engineering method, scaffolds act not only as a structural support system, but also as a conductor for cell growth. Due to the significance of the scaffold, it is imperative that the scaffold can mimic the functionality and complexity of natural tissue (Figure 3). Research is being done for other approaches to tissue engineering such as a modular approach, which involves the assembly of small cell laden modules that are combined to form larger structures. Another approach is the idea of a scaffold free approach. This approach consists of just growing cells in the lab and getting them to self-assemble into tissues [11, 12].

Current Approaches

Currently available medical products on the market utilize decellurized animal and human tissue. Humacyte is an example of a company developing lab-grown organs with subsequent decellularization. Decellularization is the process of removing cellular and immunogenic materials from tissues and organs while maintaining all the other mechanical and bioactive properties of the tissue. Think of it as doing a factory reset on a cell phone. The personal data is removed, but the phone is still physically a phone and can be passed onto another person for use. Humacyte is focused on investigational human acellular vessels that have the potential to be utilized as “off-the-shelf” human vascular grafts. In the current process being used by Humacyte, the blood vessels are formed from banked human vascular smooth muscle cells grown into blood vessels in the lab, which are then decellularized to limit the chance of immune rejection once implanted. No cells from the patient are required for this production process. However, this lab culture process can take more than eight weeks and be very costly. Data pertaining to the recently initiated clinical trial evaluating their use in angioaccess have not been reported, but the preclinical studies used to support this ongoing clinical trial do not suggest that their performance will be superior to currently available vascular grafts made from expanded polytetrafluoroethylene (ePTFE) which is more commonly known as Gore-Tex [13-15].

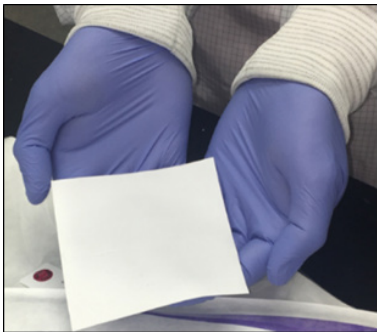

Figure 2: RenovoDerm’s Phoenix Wound Matrix for acute and chronic wounds.

Figure 3. Atreon Orthopedics’ Rotium Bioresorbable Wick used for rotator cuff repair.

Another cell-based approach to making a vascular graft is being pursued by Cytograft. Cytograft grows flat sheets of cells which they then roll into a tube to form a blood vessel. This technology and has yielded promising preclinical data and led to human clinical trials [13, 16-18]. Although these studies confirm the feasibility of using a tissue engineered vascular graft (TEVG) in humans, these cell sheet-based TEVGs have not outperformed current synthetic graft function in humans [19-21]. In fact, none of the data to date have demonstrated equivalent performance between the cell sheet TEVGs and currently available synthetic grafts.

LifeCell is another example of a company who is in the tissue engineering and regenerative medicine market. LifeCell utilizes human cadaver tissue that is processed to remove cells while preserving the essential biological components and structure of the dermal matrix to support regeneration in a product called ALLODERM SELECT™. Allograft tissue can integrate into the body and has been used in numerous clinical applications, but it is extremely costly. A small patch of material can cost several thousands of dollars and some reconstructive procedures may use up to a dozen sheets.

ParaGen Technologies’ mission is to eliminate the major problems associated with synthetic and biological implants, while incorporating the advantages of each. The core technology of Paragen Technologies is synthetic nanofiber scaffolds that mimic the physical structures in the body (Figure 1) and allow cells to assimilate and remodel into native tissue. The nanofiber scaffold acts to provide tissue level structural support to cells, thus encouraging cell adhesion to the scaffolding and proliferation. These are the key factors that enable

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tissue regeneration and prevent scar formation. ParaGen Technologies utilizes off the shelf polymers (i.e. the same polymers used in resorbable sutures) to create our nanofibers which allows us to lower the cost of the product. We process the polymers into fibers using electrospinning. Electrospinning is a relatively common manufacturing process; the novel component of ParaGen Technologies is the design of each of our scaffolds. Our scaffold technology is protected by over 50 issued and pending patents and allows for a controlled degradation profile, a tailored fiber diameter, a specific pore size, and mechanical properties that match the native tissue. We design and pick materials based on the clinical application and our devices are carefully tailored to address clinical needs for each indication.

ParaGen Technologies has launched four regenerative medicine medical device companies that are in various stages of development ranging from FDA approved devices to large animal studies. RenovoDerm is developing a portfolio of wound care devices that increase the speed of healing for chronic wounds, while decreasing scar tissue. RenovoDerm's first product, the Phoenix Wound Matrix (Figure 2) received FDA clearance and is currently being used in wound care clinics, hospitals and Veterans Affairs hospitals. Atreon Orthopedics (Figure 3) has developed a scaffold called the Rotium Bioresorbable Wick that improves the rate of healing and overall strength of repair in rotator cuff injuries. This was tested in a sheep study and received FDA clearance as well. Tarian Medical (Figure 4) is developing a scaffold product for stronger hernia repairs with less scarring and adhesions which is being tested in rabbits. Lastly, Vascular Genesis (Figure 5) is developing synthetic vascular grafts that remodel into healthy vascular tissue with a focus on vascular access grafts for patients undergoing hemodialysis. These vascular grafts are being tested in sheep with the data being presented to the FDA for an interactive review and consideration as a Breakthrough Device which will significantly speed up the process for regulatory review.

Conclusion

The field of tissue engineering is progressing rapidly and moving into the clinic. There are products currently available on the market that fall into the category of tissue engineering such as allografts and xenografts, but the lab-grown organs are still over a decade away from reaching the clinic. Additionally, there are challenges for some of these allograft materials due to the need for cold storage and short shelf life. However, there is a new class

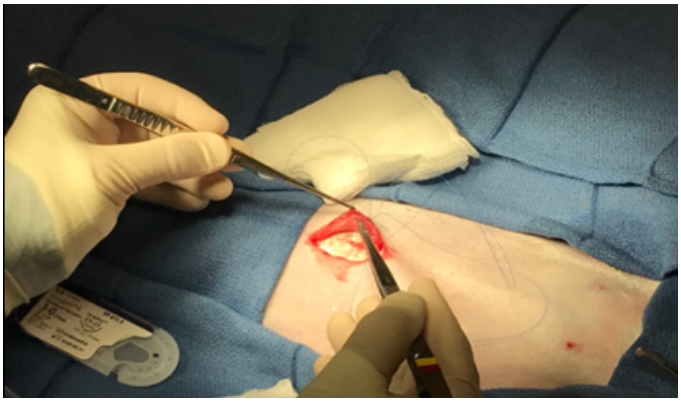

Figure 4. The Tarian Medical hernia mesh being implanted into a rabbit. chronic wounds.

of synthetic nanofiber scaffolds that are being used today for advanced wound care (i.e., the Phoenix Wound Matrix) and rotator cuff repair (i.e. Rotium Bioresorbable Wick) with a suite of products for hernia repair and vascular graft replacement following on its heels. These synthetic nanofiber grafts are stored in ambient conditions with long shelf lives. The same 'plastic' that has been used for decades in resorbable sutures is now being used to re-grow organs through a process called tissue engineering. To learn more about Nanofiber Solutions' scaffolds for tissue engineering you can view the publications listed here: https://www.ncbi.nlm.nih.gov/sites/myncbi/jed.johnson.1/bibliography/49866662/public/?sort=date&direction=ascending

The wait for organ transplants is over, and tissue engineering is here for a better tomorrow.

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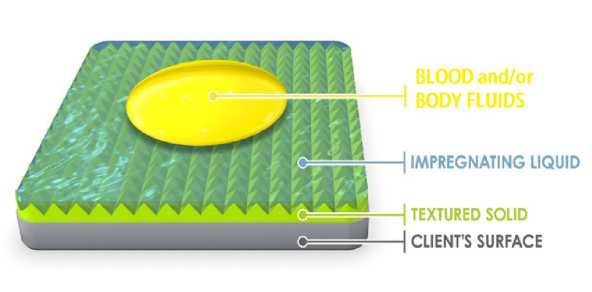

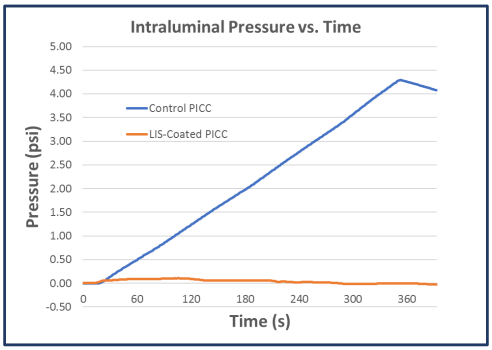

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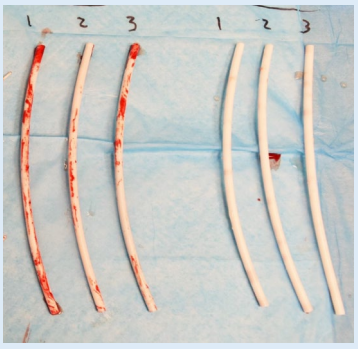

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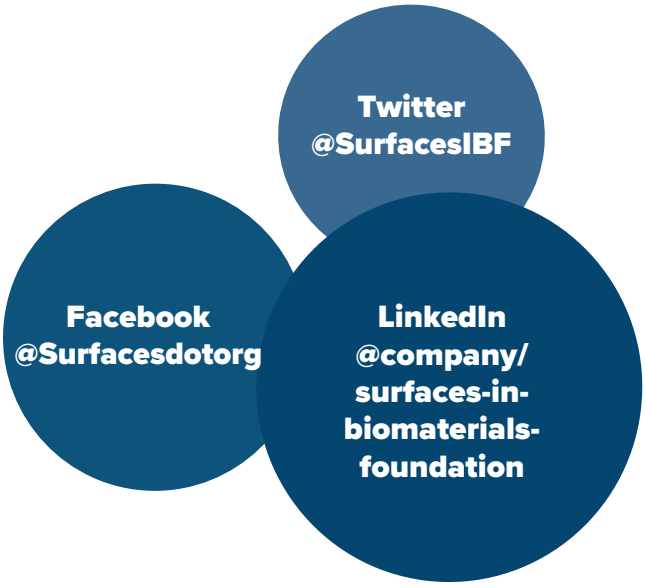

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