SurFACTS in Biomaterials

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INSIDE THIS ISSUE

From President Rob Diller

Dear Colleagues,

I am honored to serve as president for Surfaces in Biomaterials Foundation (SIBF) for the upcoming year! I consider myself very fortunate to represent our members and will work hard to meet your expectations. I would like to thank Angie DiCiccio, our outgoing president, for her service over the past two years. Angie's leadership has been integral to the success of SIBF during a challenging time for the world. I would also like to recognize the past Board of Directors and committee members for their hard work and commitment to their various roles and responsibilities over the past year. We have a lot to be proud of! I extend a warm welcome to the incoming Board of Directors and committee members—thank you for volunteering your time and committing to make 2022 another successful year for SIBF.

Our professional Foundation depends on strong investments and support from our members and sponsors. Since joining SIBF in 2010 as a student member, the Foundation has become a professional home base for me; the network of great individuals and thought leadership is unparalleled. To our current members and sponsors, thank you. I ask you to renew your commitments to our Foundation for 2022 and to help us recruit new professionals to join our mission. For nonmembers, I urge you to formalize your membership and involvement in the Foundation. We have many areas of need in 2022: Program Committee, Membership Committee, and Foundation Sponsorship. Please feel free to reach out to me directly if you are interested in getting more involved.

We successfully hosted BioInterface virtually the past two years, but we are looking forward to returning to an in-person format in 2022, Nov. 2–4, in downtown Portland, Oregon! We are planning the sessions now and will periodically update the website with details on venue hotel, abstract submission deadlines and calls for SurFACTS articles.

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From President Rob Diller

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On behalf of the Surfaces in Biomaterials Foundation, I wish you and your families a wonderful holiday season and a Happy New Year. I'll see you in Portland, Oregon, for our BioInterface 2022 Workshop and Symposium, Nov. 2–4, 2022 … mark your calendars!

Rob Diller, SIBF President
rdiller@amniotechnology.com

The Evolution of Combination Product Commercialization

By Stephen Amato, PhD, MBA, RAC

The global combination product market is currently being driven, in part, through advances in technological capability. For example, new types of biomaterials are being developed to serve as more stable and versatile implants, but also to serve as innovative local drug delivery devices. In the home healthcare market, new technologies are being developed to enable treatment providers to monitor patient care remotely through collection of medical data and administration of medication. The potential list goes on, but one thing is clear: **The combination product technologies that are being developed today are ones that we will not be able to live without in the near future.**

Although this is a wonderful development from a patient care standpoint, these significant advances in technology create issues from a market access perspective. On the regulatory front, it is nearly impossible to anticipate every potential patient safety risk that may arise from the utilization of a new type of combination product. This creates difficulty from a guidance document standpoint and places FDA and other regulatory bodies in a difficult position since they cannot be proactive in collaborating with manufacturers of such technologies. From a reimbursement and health economics perspective, how are Medicare and private payers going to compare new combination products that may, in fact, be safer and more effective for a given indication for use, with current standard(s) of patient care. Health care consumers and patient advocacy groups demand rapid access to technological innovation, while at the same time insist on maximization of safety at minimal cost.

In spite of what might seem to be dire market conditions, medical device, pharmaceutical and biologic product manufacturers continue to develop new combination treatments without clear regulatory or reimbursement pathways. The FDA does offer guidance documentation to these stakeholders, but such guidance is subject to interpretation and may be perceived as unclear, for the aforementioned reasons. Similarly, Medicare and other third party payers do not consistently apply coverage policies to new technologies, and even when they do, coding mechanism(s) may not exist and payment levels may be widely variable.

As a result, combination product developers need to consider the following strategies while commercializing their treatments:

Know the development of a regulatory pathway for combination product market access

The existing process for FDA approval involves classifying combination products as one of four different types. Combination product developers need a strong understanding and rationale for pursuing one pathway versus another. This can involve a bit of a negotiation, with FDA, and manufacturers may be able to take advantage of certain regulatory strategy incentives depending on the pathway.

Don't be afraid to launch products in generations

This approach can be very useful with combination products. For example, manufacturers of unique cellular scaffold biomaterials can first worry about launching the scaffold as an implant support device. If developed properly, stem cells or other cell types could be added to provide further support, or even promote the development of soft tissue or other anatomical structures in the next product generation.

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The Evolution of Combination Product Commercialization ...

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Develop strong clinical development endpoint strategies

The FDA doesn't have existing or universally acceptable clinical development strategies and end points for certain type of combination products. Take the iPhone for example—before its release everyone survived without it, but had to carry around two devices: a mobile phone and an iPod. Imagine if the iPhone were being assessed for clinical safety and efficacy prior to its commercialization. Without direct technological comparators on the health market, development of clinical endpoint strategies for combination products can be extremely difficult. Thus, manufacturers should negotiate with, but not depend on, FDA to develop clinical endpoint strategies for highly innovative, yet cutting edge and potentially risky combination products. Instead, they should utilize their understanding of regulatory science principles, as well as their desired indication(s) for use to carefully construct such endpoints.

Understand pricing and reimbursement

Combination products involve advanced technologies, so they can be, by their very nature, expensive relative to current standard of care. Therefore, while product pricing should be value based versus cost plus based, pricing can be a difficult challenge for many combination products that don't have a comparable product on the market. As a result, an understanding of the health economic and potential payer landscape is a critical part of the combination product commercialization planning process. Manufacturers should talk to payers, they should understand what comparative and cost effectiveness research will be required to optimize market penetration, and they should work with patient advocacy groups to create demand for their combination product long before it is approved from a regulatory perspective.

The combination product market, with its cutting edge technological advancements, is an exciting one to follow. All of us are potential patients, and we should be greatly enthused at the prospect of having what we now might not consider possible, to be an indispensable part of our care as we move on through our lives. However, manufacturers face what some might perceive to be insurmountable challenges during the combination product commercialization process, including patient safety and cost utilization concerns. Yet, through careful planning and proactive collaboration among healthcare stakeholder groups, new combination products may revolutionize and even create new segments in the global healthcare marketplace.

An Overview of Medical Device Clinical Trials: Classification & Challenges

Theresa Enright and the Subject Matter Experts at PharPoint Research

Medical devices make up a substantial segment of our healthcare operations for the diagnosis and treatment of health conditions. The creation and approval of new devices is important to the continued improvement of the overall health, improved diagnosis, and availability of treatment options for patients.

Section 201(h) of the Food, Drug and Cosmetics Act defines a medical device as "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory...which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes." This includes implantable devices and devices designed to deliver a drug or biologic to a patient. In the latter case, the drug or biologic being delivered is usually evaluated separately by the FDA Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER), while the FDA Center for Devices and Radiological Health

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An Overview of Medical Device Clinical Trials: Classification & Challenges ...

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(CDRH) evaluates medical devices.

Unlike requirements for investigative drug/biologics products, only a small percentage of devices require clinical data to demonstrate they are both safe and effective prior to market approval. The FDA classifies medical devices into Class I, II, and III. Most medical devices can be classified by finding the matching description of the device in Title 21 of the Code of Federal Regulations (CFR), Parts 862-892. For each of the devices classified by the FDA the CFR gives a general description including the intended use, the class to which the device belongs (i.e., Class I, II, or III), and information about marketing requirements. Most low-risk devices may be marketed without prior FDA review, and most medium-risk devices must only determine substantial equivalence to an existing device. However, certain Class II devices and all Class III devices which pose a significant risk of illness or injury must go through the FDA's Premarket Approval (PMA) process to evaluate safety and effectiveness.

The PMA process requires manufacturers submit clinical data assuring the safety and effectiveness of a device. This process is similar to (although typically less robust than) the clinical trial process for investigative drugs/biologics.

Medical device clinical studies are usually categorized as feasibility studies or as pivotal studies. A feasibility study may provide support for a future pivotal study or may be used to answer basic research questions. These studies are not intended to be the primary support for a marketing application. In feasibility studies, endpoints and sample size are generally not statistically driven, and studies average 10–40 patients. Pivotal medical device studies, however, are intended as the primary clinical support for a marketing application and must be designed to demonstrate a "reasonable assurance of safety and effectiveness."

Medical device trials also have the potential to encounter a number of challenges that are unique from drug/biologic studies:

- Blinded, randomized, controlled trials (RCTs)—the gold standard design for drug trials—are rare within medical devices trials, as device trials are often very difficult to blind.

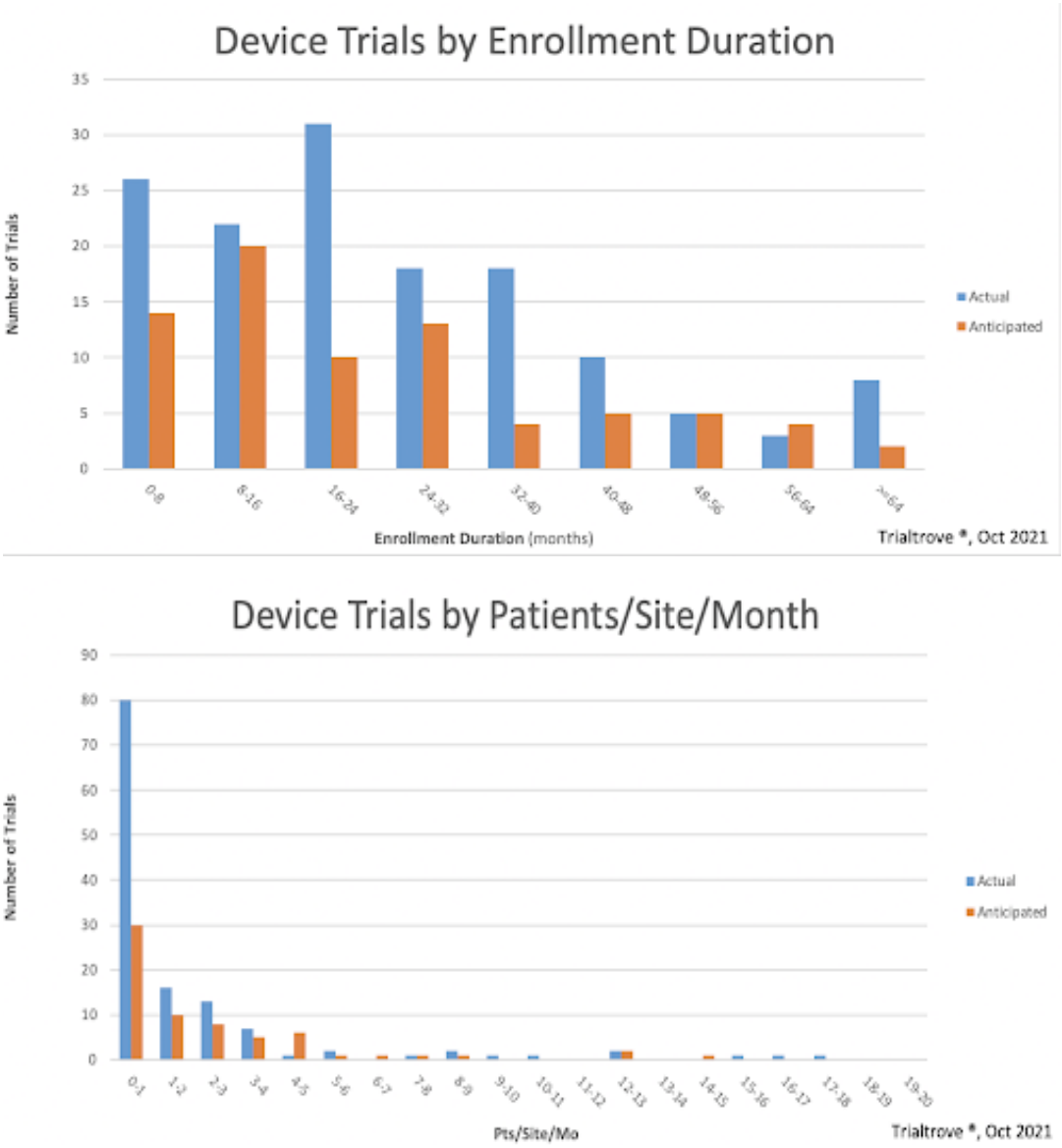

Figure 1. Top—Device trials by enrollment duration, anticipated vs. actual duration. Bottom—Device trials by patient per site per month. Data collected using Pharma Intelligence (https://pharmaintelligence.informa.com/)

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- Developing sham devices and procedures is complicated, and in certain scenarios may be considered unethical. However, mounting evidence has shown that medical procedures can create a strong placebo effect, and sometimes a comparative placebo arm is required by the FDA for approval.
- Resulting data depend heavily on physician technique. This amplifies the importance of proper, thorough, and timely investigator/site training along with strategic selection to ensure physicians have the right guidance, tools, and qualifications to use investigative devices in the way device companies intended them to be used.
- Device studies often include highly diverse endpoints.
- Modifications may be made to an investigational device during a clinical trial.

The data displayed in Figure 1, collected from Pharma Intelligence Informa's Citeline tool, show average of enrollment duration and the average patients per site per month rate for device trials.

As with clinical trials focused on novel drugs and biologics, low or slow enrollment may occur if sites are not selected strategically and properly managed. Site feasibility assessments and a strategic site selection process can help predict speed of enrollment and how data flow will occur over time, considering areas such as past performance, site qualifications/ experience, access to patient population, and operational excellence.

About PharPoint Research

PharPoint Research is an award-winning, client-focused contract research organization that offers project management, clinical operations, data management, biostatistics and statistical programming, and strategic clinical trial consulting services to clients of all sizes. For more information about the PharPoint team, visit pharpoint.com.

Biointerface Student Session Summary

Natalie Petryk: First place winner

Over two years ago, I started working in Dr. Mary Beth Monroe's lab as an undergraduate student simply wanting to gain more research experience. Never did I think my research in her lab would translate into the love and passion for biomaterials-related research that I have now. Now, as a bioengineering master's student in the Monroe Biomaterials Lab, I have been able to further explore my research interests and build upon exciting work that I was fortunate to present in the BioInterface Student Pitch Competition.

Having the opportunity to share my current research as part of the BioInterface Student Pitch Competition was a fun, invaluable experience that I am grateful to have taken part in. It was fascinating to learn more about advances being made in biomaterials research and industry from both students and professionals in the field. Presenting my research in the form of a pitch truly allowed me to reflect on the significance of my work, because I was focused on conveying its potential impact to a broader audience. Overall, attending the BioInterface Workshop and delivering my pitch confirmed my interest in biomaterials and my future career goals.

Polyurethane shape memory polymer (SMP) foams are "smart" materials that can switch between a primary and secondary, deformed shape when exposed to an external stimulus.[1] This behavior allows SMP foams to have wide-ranging biomedical applications in areas such as drug delivery, tissue engineering, and wound healing; in these applications, tuning the pore structure of SMP foams can greatly affect drug release rate, cell proliferation and migration, and hemorrhage control, respectively.[2]–[5] The ease of tuning both pore size and interconnectivity could greatly aid in future commercialization efforts of SMP foams for multiple uses. My work explored off-the-shelf solvents and their use as physical blowing agents to safely and easily tune pore structure.

Physical blowing agents are incorporated during foam synthesis, and unlike chemical blowing agents, they do not affect foam chemistry; they boil off during foaming, forming bubbles that result in pores throughout the polymer.[6] Enovate is a physical blowing agent commonly used in gas-

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Biointerface Student Session Summary (Natalie Petryk) ...

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blown foaming, but the Environmental Protection Agency (EPA) considers its use unacceptable because it is a hydrofluorocarbon that can contribute to global warming.[7] It also comes from a single supplier, making commercial use risky.

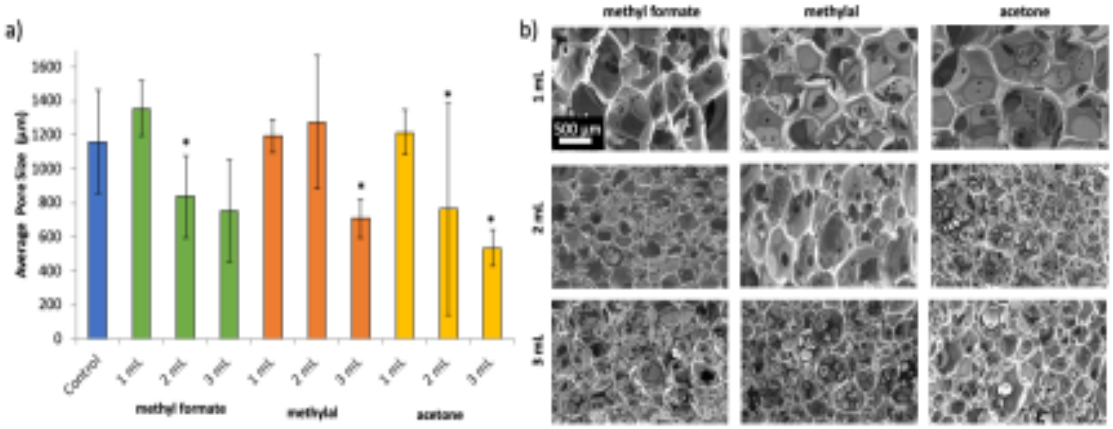

Figure 1: Foam pore size and morphology. (a) Average pore size (µm) for control foams and foams containing 1 mL, 2 mL, or 3 mL of methyl formate, methylal, or acetone. *p < 0.05 compared to control foam. (b) SEM micrographs showing pore morphology and interconnectivity of all foams in (a). Scale bar applies to all images.

We selected three physical blowing agents that are both commercially available and recommended for use by the EPA in their Significant New Alternatives Policy (SNAP) Program: acetone, dimethoxymethane (methylal), and methyl formate. [8] We found that increasing the volume of solvent added during foam synthesis (1 mL, 2 mL, and 3 mL) increased the interconnectivity between pores while maintaining chemical and thermal properties of the SMP system (Figure 1). We also saw a general decrease in pore size with increased solvent volume. This work provides a safe and easy method to create a more open, porous structure that could be tailored for different applications.

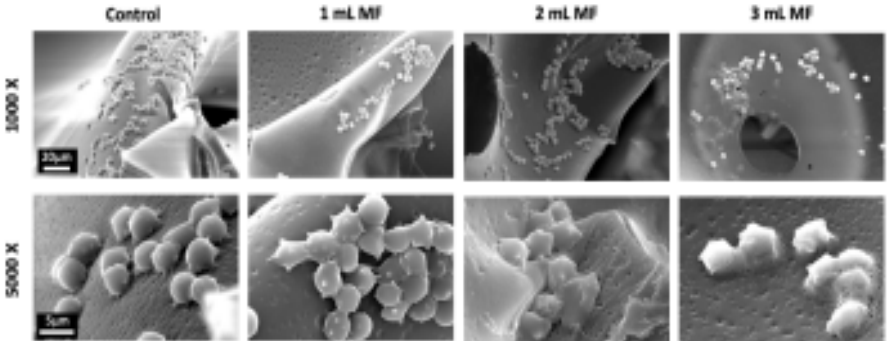

Figure 2: Platelet attachment to and activation on control and methyl formate (MF) foams. Thrombus evident in 2 mL and 3 mL MF foams. Scale bar applies to all images in a row.

More recently, I explored the effects of tuning foam pore structure on blood and cell interactions with foams synthesized with methyl formate. We found that foams with more interconnects (i.e., synthesized with a higher volume of methyl formate) had thrombus formation after one hour of incubation in anticoagulated blood (Figure 2), which suggests that the clotting ability of these foams could be harnessed in traumatic wound healing applications. We also saw that larger pore size and fewer interconnects among control foams and foams synthesized with 1 mL methyl formate resulted in higher cell attachment (Figure 3). This result could be an effect of the higher overall surface area that cells could attach to, an important consideration for designing tissue engineering scaffolds.

Future work involves synthesizing a completely off-the-shelf foam to make the commercialization of polyurethane SMP foams more feasible. This research will require substituting our current single-supplier catalysts with commercially available options, as well as synthesizing our own surfactant with off-the-shelf components. I also hope to look at blood perfusion through foams with different levels of interconnectivity and eventually explore vascularization as a function of foam interconnectivity.

My work in the Monroe Biomaterials Lab has opened my eyes to the potential of biomaterials. I am extremely thankful for Dr. Monroe's support and guidance over the last 2 and half years, as my research under her has shaped my future career goals; after completing my master's, I plan to pursue a Ph.D. and eventually work in industry doing biomaterials R&D.

I would also like to thank and acknowledge Grace Haas and Anand Vakil for their help with this project. Lastly,

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Biointerface Student Session Summary (Natalie Petryk) ...

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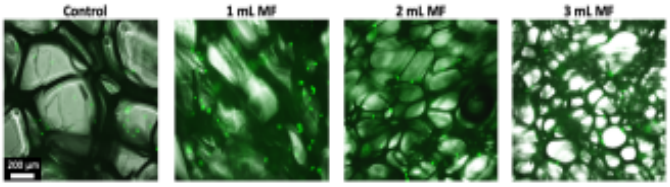

Figure 3: Brightfield and GFP overlay images of cell attachment to control and methyl formate (MF) foams. Scale bar applies to all images.

I am thankful for opportunities like the BioInterface Student Pitch Competition to be able to share my work with broader audiences that are also passionate about biomaterials.

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[8] "Substitutes in Flexible Polyurethane | US EPA." https://www.epa.gov/snap/substitutes flexible-polyurethane.

Samuel Briggs: Second place winner

I would like to thank the Biointerface planning committee for the opportunity to participate in the student pitch competition. This was a unique, industry-relevant, format in which to present my research.

In my pitch, I presented my graduate work entitled "Characterization of an Electrospun Polyurethane with Tunable Chemistry and thiol-ene Crosslinking for Biomedical Applications." In this work, we developed a novel class of material that incorporates vinyl sidechains into the backbone of a thermoplastic shape memory polyurethane. This functionality enables us to solution blend this material with a poly-thiol crosslinker and initiate crosslinking post-fabrication into the desired geometry. We combined this versatile polymer system with the fabrication technique of electrospinning. Electrospinning is advantageous for biomedical applications due to the micro-fibrous morphology of the deposited material with unique mechanical and biological properties. The ability to direct microfiber alignment allows us to generate anisotropic material while the scale of the fibers can closely mimic the extra-cellular matrix of many tissues. Our polymer system fits well with the electrospinning technique because electrospinning requires a starting thermoplastic material that can be dissolved in a solvent and extruded through a needle. However, by incorporating this thiol-ene crosslinking mechanism we could fabricate the desired micro-fibrous morphology and then crosslinking via UV exposure, giving us a thermoset final material with improved mechanical and shape memory properties. During the study, we discovered that we could dramatically improve the crosslinking efficiency within electrospun materials by swelling them in dilute acetone during UV exposure. This allowed molecular mobility during crosslinking without destroying the fibrous architecture. This process allows

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Biointerface Student Session Summary (Samuel Briggs) ...

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us to fabricate this shape memory polyurethane into the desired morphology via electrospinning and then crosslink the material for enhanced properties. These enhanced properties widen the door of potential applications for this material. Potential applications for this shape-memory material include anastomosis repair, bone defect stabilization, or tendon repair.

My work on this project has given me the opportunity to learn several industry-relevant skills. I utilized Solidworks to draw and 3D print parts when constructing the electrospinning setup utilized. In determining the ideal electrospinning parameters, I utilized a Design of Experiments (DOE) approach with JMP statistical software. I have had the opportunity to interview multiple physicians across many fields regarding potential devices to help direct applications of this material. Additionally, I have had the assistance of many undergraduate researchers on the project and learned management techniques while working with them. As I imagine is the case for many Ph.D. students, the lessons of this project have extended far beyond what I initially expected.

Background information on Samuel

Undergraduate institution: Utah State University

Undergraduate research: Electrospinning of Spider silk under Dr. Randy Lewis

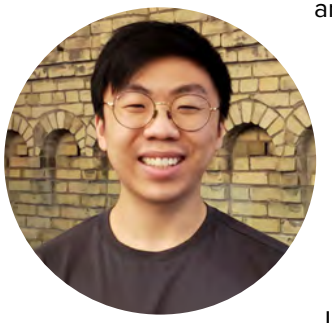
Graduate institution: Texas A&M University

Graduate research: Electrospun Shape Memory Polymers in the Biomedical Device Laboratory under Dr. Duncan Maitland.

Internships: GE Healthcare Life Sciences and Gore Medical

Hobbies: Rock climbing/routesetting, woodworking, Basketball, absurd dancing with my children

Chris Ling: Third place winner



I would like to first thank the committee of the Surfaces in Biomaterials Foundation for organizing a great online conference! I really appreciated that the sessions were spaced out and recorded so that I would be able to watch sessions that conflicted with other events in my school schedule. As a graduate student who is interested in translational research and the development of medical devices, many of the sessions were eye-catching and insightful, especially the Medical Device Pioneers workshop. I'm looking forward to the in person conference next year where I would be able to meet, talk, and exchange ideas with presenters and other attendees.

Participating in the student pitch competition was a fun and insightful experience for me as a relatively new graduate student. It got me thinking about how to frame my project and pick the more relevant or exciting data to fit within the time limit. Coming in third place was a pleasant surprise after watching some of the other great student pitches and I'm grateful to the judging committee for their selection. Since the student pitch was online and asynchronous, I wasn't able to receive any feedback or questions but I'm hoping to be able to do so at the next conference where I can interact with others during the event.

I'm excited to continue the research that I presented at the conference for developing liver tissue engineering methods. Currently, I'm working on the development and evaluation of a material for the 3D encapsulation of bile duct cells in the hopes of generating self-assembled bile duct tissue. I would then be interested in using these self-assembled structures for the development of a disease or drug screening model. If things pan out well, I'm hoping to present some exciting results that could be shared for the next conference!

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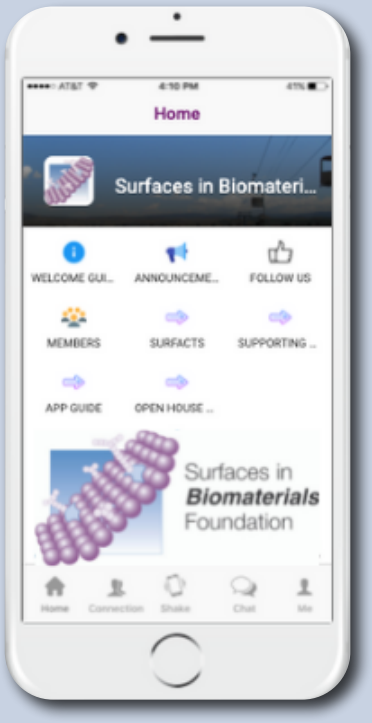

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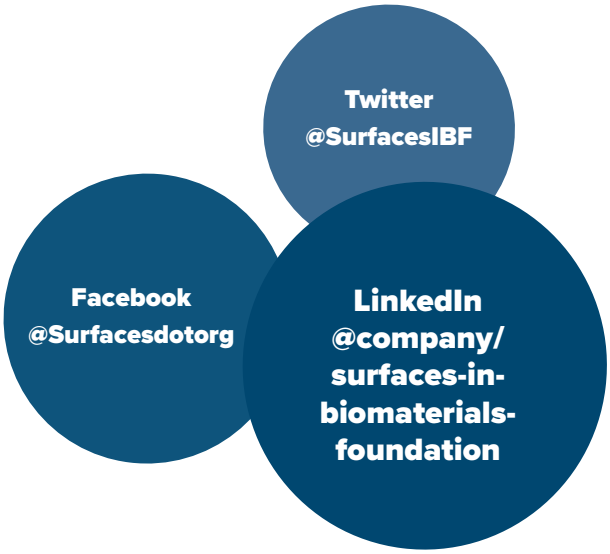

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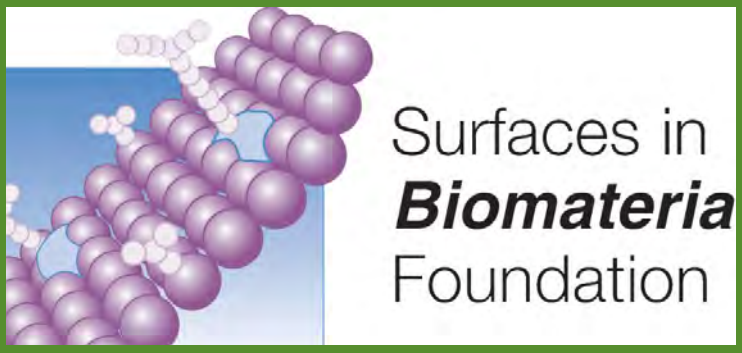

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