SurFACTS in *Biomaterials*

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From the Editor

By Joe McGonigle, SurFacts Executive Editor

I have just a few quick items to announce this month. The first is that Bill Theilacker from Medtronic is stepping down from serving as the Surface Characterization and Analysis editor for SurFacts. I extend my thanks to Bill for all his hard work on the newsletter in the past few years. We are currently looking for someone from a member organization to fill his role.

I'd also like to welcome Jaishankar Kutty from Saint Jude to the SurFacts editorial team. Jai will be acting as a Medical Device Editor and will be contributing articles about devices of interest to the biomaterials and surface science field.

Jaishankar is a Senior R&D Scientist at St. Jude Medical, Inc. and his contributions in this role range from that of a technical expert enabling new generation transcatheter tissue heart valve development to creating novel testing strategies as part of a newly developed advanced biomechanics lab. He joined the company in 2008 and at the time he was involved in developing novel strategies to effectively characterize collagen-based tissue and appropriately tailor the material properties to suit surgical and transcatheter heart valve design and durability requirements.

In 2008, immediately following graduation from Clemson Bioengineering he honed his skills in soft tissue biomechanics with an internship stint at Bose ElectroForce. While at Clemson (2003-2008), his research was aimed at demonstrating proof-of-concept using relevant prototypes for wound healing/drug delivery applications by creating polymer-based scaffolds with tunable properties for functional tissue regeneration via tissue engineering approaches.

Jaishankar began his career with GE Healthcare (formerly Wipro GE Medical Systems) as an Applications Engineer in Mumbai, India. He holds a Bachelor of Engineering in Biomedical Engineering from D.J. Sanghvi College of Engineering, University of Mumbai, India. He grew up in Mumbai and is a native of Kerala, India. In his spare time, Jaishankar enjoys playing cricket, soccer, listening to and playing music, reading, and traveling with family/friends.

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Members are encouraged to submit articles for future editions of SurFACTS. Please e-mail your report (with all appropriate figures and graphics) to Staff Editor Jazzy McCroskey at jasperm@ewald.com for consideration in a future issue. Deadlines for upcoming issues are posted on surfaces.org.

Member News

Boston Scientific received FDA approval for the Promus PREMIER™ Everolimus-Eluting Platinum Chromium Coronary Stent System, a next-generation drug eluting stent. The new stent offers improved visibility along with ease of deliverability and strength. Drug elution is controlled using a biocompatible fluorinated polymer. The company also received a favorable vote from an FDA advisory panel regarding its WATCHMAN™ Left Atrial Appendage Closure Device and expects FDA approval sometime in 2014.

W.L. Gore announced FDA approval of the GORE® VIABAHN® Endoprosthesis for Revision of stenosis or thrombotic occlusion with AV hemodialysis access grafts. The device has long been used in the iliac and femoral arteries and features an ePTFE liner attached to a nitinol stent and is coated with the **CARMEDA**® BioActive Heparin Surface (CBAS® Heparin Surface).

American Preclinical Services opened a third cardiac cath lab suite to provide companies with better scheduling options. The new suite features state of the art equipment as well as video streaming and nearby spacious conference rooms for monitoring procedures.

Bausch + Lomb announced FDA clearance for its newest replacement silicone hydrogel contact lenses made with MoistureSeal™ Technology. This represents first new innovation in frequent replacement silicone hydrogel technology in seven years.

Saint Jude Medical began two new US studies in December. The first, SENSE (Subcutaneous and Epidural Neuromodulation System Evaluation), is evaluating a combination of peripheral nerve and spinal cord stimulation to treat low back and leg pain. The second, SUNBURST™ (Success Using Neuromodulation with BURST), will test the Prodigy™ neurostimulator which delivers a proprietary mode of stimulation therapy for chronic pain.

Covidien presented positive data from two clinical trials in the peripheral artery space. The first was the final results from the DURABILITY II study of its EverFlex™ self-expanding stent which showed a low need for repeat procedures and low rates of stent fracture. The second was initial results from the DEFINITIVE AR study which compared directional atherectomy with the TurboHawk™ plaque excision system in combination with drug-coated balloons to use of drug coated balloons alone. Early results indicate improved lumen gain with fewer tears and bailout stenting for the combination treatment. Covidien also announced that it will be exiting its OneShot™ renal denervation program due to slower than expected growth in the market.

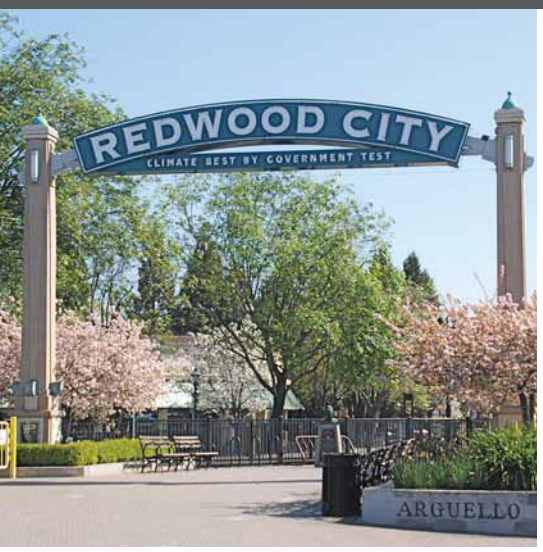
ExThera Medical announced that its Seraph® Microbind® Affinity Blood Filter has demonstrated the ability to remove a broad range of pathogens and toxins from blood and that positive data will be presented at the Critical Care Congress in San Francisco in January, 2014.

DSM Biomedical announced that is partnering with BiO2 Medical to provide its ComfortCoat® Coating for the Angel® catheter intended to provide IVC filter protection for pulmonary embolism. The catheter incorporates a nitinol filter attached to a triple lumen central venous access catheter and the coating facilitates ease of placement and reduced vessel trauma. DSM also announced the opening of a new facility to provide coating services to its customers.

Member News continues on pg. 5

SurFACTS in Biomaterials is the official publication of the foundation and is dedicated to serving industrial engineers, research scientists, and academicians working in the field of biomaterials, biomedical devices, or diagnostic research.

Save the **Date!**



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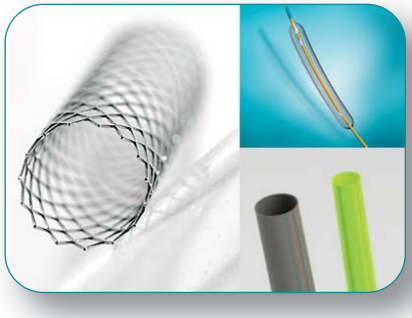

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Communication by: Partridge Design

Member News continued from pg. 2

Medtronic received early FDA approval for its transcatheter CoreValve® system which demonsrated low rates of stroke and leakage in a pivotal clinical trial. They also announced that the primary endpoint for efficacy was not met in the SYMPLICTY HTN-3 trial of its renal denervation technology, despite showing safety.

Anton Paar acquired CSM Instruments and will continue to run the company as a subsidiary under its former name. Anton Paar is a global provider of laboratory instruments, process instrumentation, custom automation and robotics solutions based in Graz, Austria.

Physical Electronics unveiled the PHI X-tool an automated XPS probe designed to make it easy for users to perform small and large area XPS measurements. They also released the 710 Scanning Auger Nanoprobe which will give users improved capabilities.

Transcatheter Aortic Valve Implantation (TAVI) Devices in Brief

By Jaishankar Kutty, PhD, SurFacts Medical Device Editor

Bioprosthetic Heart Valves

The use of tissue heart valves has increased dramatically since the 1990s, primarily due to the increased risks of bleeding associated with the lifelong use of anticoagulants for mechanical heart valves. However, structural valve deterioration which is the most common complication associated with tissue valves, necessitates re-operation for replacement of the degenerated bioprosthesis and is associated with increased morbidity and mortality rates.

What's special about TAVI?

Eleven years following the first implant by Dr. Alain Cribier in April 2002, transcatheter aortic valve implantation (TAVI) procedures demonstrate outcomes similar to surgery in high-risk patients and superior results in inoperable patients compared to conventional medical therapy. The most intuitive advantages are the avoidance of sternotomy – the valve is delivered through the femoral artery (transfemoral) or the apex of the heart (transapical), cardiopulmonary bypass, and minimal hospital residence times. However, while the benefit is apparent in high risk patients, the improvements in quality of life and cost-effectiveness of TAVI in comparison with surgical aortic valve replacements remain uncertain, in lower risk patients. With the FDA approval of the Edwards Sapien valve (transfemoral/transapical) (Edwards Lifesciences, Irvine, CA) in 2011 and the CoreValve TAVI device (transfemoral) (Medtronic, Inc., Minneapolis, MN) expecting FDA approval sometime in 2014, this fast evolving field of TAVI devices is poised to become the front runner in alleviating severe aortic stenosis in patients deemed too high risk for surgical aortic valve replacements.

First generation TAVI Technology & Shortcomings

Conventionally, TAVI technologies are focused on using either a balloon-expandable stent (Stainless Steel- or Cobalt Chromium-based) or a self-expandable stent (Nitinol-based) design with bovine or porcine pericardium valve leaflets with a catheter-

based transapical or transfemoral approach for valve delivery. Importantly, neither the calcified (stenotic) leaflets nor the calcified native valve annulus is excised/debrided prior to TAVI deployment. Infact a balloon valvuloplasty is performed in most cases followed by TAVI deployment (with or without rapid pacing) with the stenotic anatomy functioning as the anchoring site for the TAVI prosthesis. Most first generation TAVI valves appear similar in design with the supravalvular "aortic" crown and the lower "annular" crown. Some of the major concerns with first generation TAVI procedures are paravalvular (PV) leak, coronary obstruction, strokes, and heart block (requiring pacemaker implants), valve migration and embolization, and vascular anatomy complications,. A combination of critical factors such as valve sizing, procedural ease, anatomical complications (such as vessel tortuosity and compliance), patient selection based on risk profiling, and post procedural patient management strategies significantly impact final outcomes.

Second Generation TAVI Technologies & Distinguishing features

Apart from the Sapien valve and the CoreValve device there are a number of innovative second-generation TAVI prostheses exploring unique design strategies specifically geared towards a smaller delivery catheter profile (18F or less), simplified anatomical positioning/alignment and device retrieval techniques. While most second generation TAVI devices continue to use bovine or porcine pericardial leaflets sewn onto metallic stents (self- or balloon-expandable) or fabric-based support structures, these devices have very strong distinguishing features.

These TAVI technologies range from those having received CE mark (namely, Symetis **Acurate** Valve (transapical) (Symetis, Ecublens, Switzerland), **Portico** Valve (St. Jude Medical, Inc., St. Paul, MN), **Direct Flow** (Direct Flow Medical, Inc., Santa Rosa, CA), **Engager** (Medtronic, Inc., Minneapolis, MN), **Lotus** Valve (Boston Scientific Corporation, Natick, MA), and **JenaValve** (JenaValve Technology GmbH, Munich, Germany) to those with first in-human proof of concept experience (namely, Symetis **Acurate** Valve (transfemoral) (Symetis, Ecublens, Switzerland), **Heart Leaflet Technology** valve (HLT Inc., Maple Grove, MN), to early stage conceptual development like the Colibri TAVI system (Colibri Heart Valve, LLC, Broomfield, CO).

The upcoming version of the **Sapien 3** device promises a taller stent frame with a Dacron skirt targeting reduced PV leaks. Edwards Lifesciences is also developing the **Centera Valve**, a self-expanding re-sheathable valve. Currently, Medtronic is also developing a second generation CoreValve called the **CoreValve Evolut** which has a shorter stent and design features to reduce PV leak.

The **Portico valve** (24F transapical & 18F transfemoral) is designed to be fully resheathed and repositioned which enables physicians to fine-tune valve placement, real time during implantation. Importantly, the bovine pericardium leaflets are located low on the Nitinol self-expanding stent thus minimizing device protrusion into the left ventricular outflow tract, thereby minimizing PV leak and heart block events. The stent features a large cell size which is designed to enable easy access to the coronary arteries and minimizes the risk of a strut transiently resting on a calcified nodule thus avoiding chances of late stage valve embolization.

Direct Flow's unconventional design supplants the often used metal stent with a Dacron-based support structure comprising unique supravalvular aortic and ventricular cuff-like rings that can be manipulated independently for repositioning and retrievability. After appropriate placement, the positioning lumens are filled with a polymer-based hardening compound to form the valve support structure.

The **Lotus** valve, from Boston Scientific, consists of three arms that guide alignment during valve deployment; the device expands in diameter thus imparting the necessary increase in radial force during anchoring. A polyurethane sealing membrane coated on the annular/anchoring end of the prosthesis serves to minimize PV leak. It is fully retrievable until final deployment and during deployment the valve is locked into place using a buckle mechanism on the stent frame. The Engager TAVI device has a self-expanding stent and a polyester skirt which is designed to minimize PV leak. The "arms" on the stent anatomically align the valve in the aortic sinuses and envelope the native leaflet to provide the necessary radial force for adequate anchoring.

The **Acurate Valve** (self-expanding) has a polyester skirt designed to minimize PV leak in addition to flexible stabilization arches that extend into the aortic

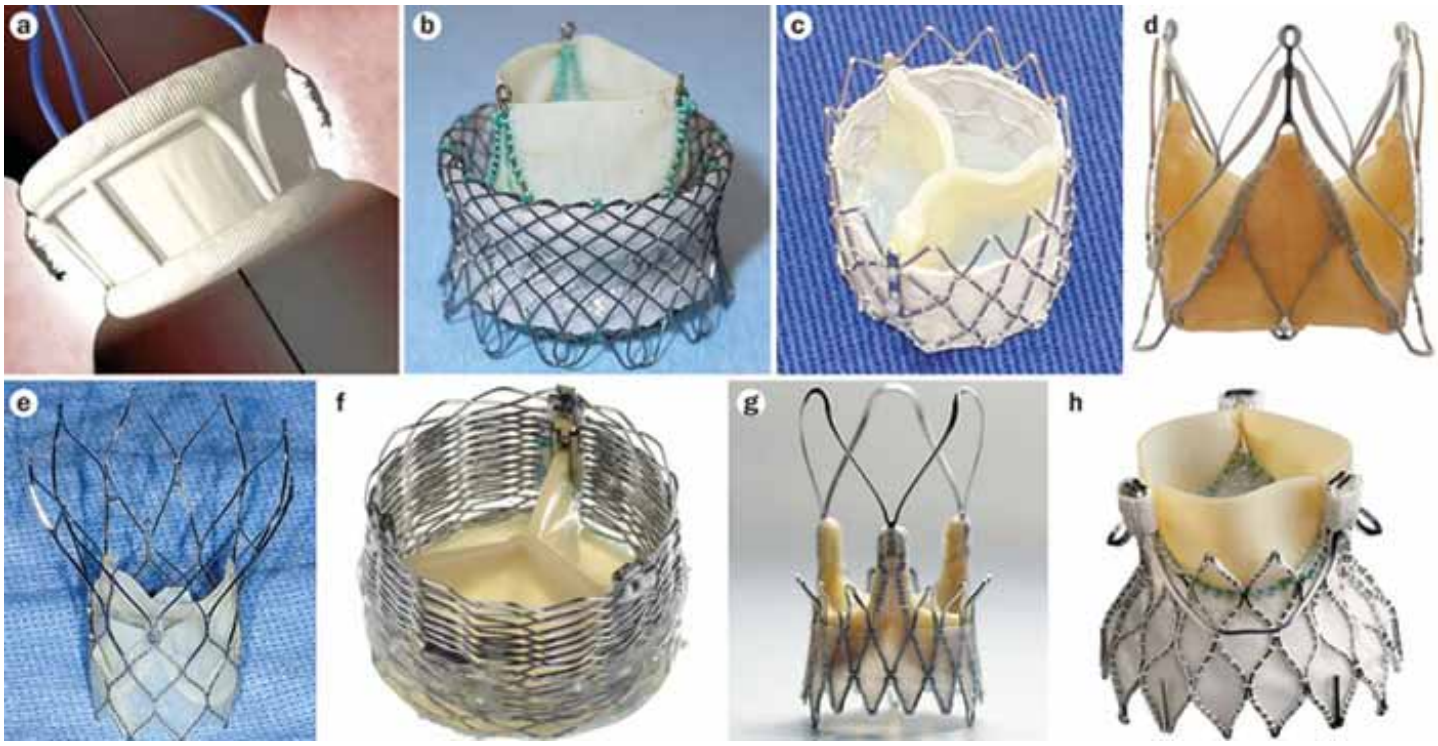

Image Source, Nature Reviews Cardiology 9, 15-29 (January 2012)

Images of Emerging Transcatheter Valves

a| Direct Flow Medical® (Direct Flow Medical, Santa Rosa, CA, USA) valve. Permission obtained from Direct Flow Medical. **b** | HLT (Heart Leaflet Technologies, Maple Grove, MN, USA) valve. ©2011 HLT, Inc. a Bracco Group Co. **c** | Innovare (Braile Biomedical, São José do Rio Preto, Brazil) valve. Courtesy of Diego Gaia, Federal University of São Paulo, Brazil. **d** | JenaValve® (JenaValve Technology, Munich, Germany). Permission obtained from JenaValve Technology. **e** | Portico® (St-Jude Medical, St Paul, MN, USA) valve. **f** | Sadra® Lotus Medical (Boston Scientific SciMed Inc, Maple Grove, MN, USA) valve. ©2011 Boston Scientific Corporation or its affiliates. All rights reserved. Used with permission of Boston Scientific Corporation. **g** | Symetis® Accurate (Symetis SA, Lausanne, Switzerland) valve. Permission obtained from Symetis. h | Engager® (Medtronic Inc., Minneapolis, MN, USA) valve. © 2010 Medtronic, Inc. Image provided by Medtronic, Inc.

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root and maintain optimal positioning once the valve is implanted. Similarly, the self-expanding **JenaValve** has a clip system to anatomically orient the device and to lock the native leaflets between the clip and the stent frame to allow for optimal sub-coronary positioning. Currently, the JenaValve is the only TAVI device to be indicated for treatment of both aortic stenosis and aortic insufficiency.

The **Heart Leaflet Technology valve** consists of porcine pericardium leaflets sewn onto a self-expanding Nitinol stent and a polyester liner to minimize PV leak. Interestingly, this unique design enables separation of the valve elements from the stent during delivery thus resulting in a relatively lower profile (17F) device.

The **Colibri** TAVI System delivered through a 14F sheath, comprises a pre-mounted, pre-packaged, pre-crimped, dry tissue technology based transcatheter valve designed for both aortic and pulmonary applications which lends itself to both the balloon- and self-expandable paradigms. In what is touted to be a third generation TAVI device, Transcatheter Therapeutics GmbH claims that the Trinity aortic valve can not only be positioned precisely but also can be fully repositioned after full implantation (unlike second-generation TAVI systems).

From a competitive landscape perspective, it may be very confusing given the number of contenders. But for an American physician/patient, the choice is fairly straightforward; the only TAVI device approved in the US is the Sapien Valve (Edwards Lifesciences), for use in high risk/inoperable patients. In Europe, however, though the use of TAVI devices is limited to the high risk/inoperable patient pool, the battle is intense with multiple TAVI devices having received the CE mark. After over 6 years of implants in Europe, at TCT 2013, Medtronic stated that approximately, 25% of extreme risk patients were ineligible for transfemoral TAVI due to vascular anatomy complications. However, the company claims that TAVI was still a viable option for

these patients with a projected high likelihood of success by employing alternative access approaches such as transaortic (incision through the aorta) and trans-subclavian (through the subclavian artery below the collar bone). Medtronic intends to seek approval for these approaches as part of its Extreme Risk submission to the US-FDA.

To date, none of the TAVI valves are perfect and no single valve has emerged as a gold standard. In addition to deliverability, retrievability, and positioning, long term durability remains one of the biggest questions that are currently unanswered. Given the sheer number of companies in the mix, the TAVI race resembles a “survival of the fittest” contest and in my opinion, the next decade will produce five TAVI valves that a physician can confidently choose from. Future areas of innovation will include technologies specifically geared towards improved durability, easier delivery/positioning/retrieval, lower profile, alleviation of bicuspid aortic valve stenosis, TAVI for aortic insufficiency and subsequent left ventricle remodeling, refined valve-in-valve technology, and transcatheter mitral valve replacement approaches. Meanwhile, successful tackling of long term durability, excessive incidence of strokes, PV leak, heart block, and patient-prosthesis mismatch by improved design and enhanced imaging techniques will enable extending the use of this technology even in low risk patients.

In vitro Testing of Tropoelastin and Collagen Electrospun Scaffolds

BioInterface 2013 Student Poster Award Winner

By Robert Diller[1], Hans Machula[1], Jeff Watson[1], Audrey Ford[1, 2], Brent Nelson[2], Robert Kellar[1, 2].
[1]Northern Arizona University, Department of Biological Sciences
[2]Northern Arizona University, Department of Mechanical Engineering

Repairing damaged tissues and organs often requires the use of replacement tissues or biomaterials. In the case of biomaterials, they must undergo biocompatibility testing prior to their clinical use. For example, biomaterials must appropriately interact with living cells as well as mimic the native biology and mechanics of the recipient tissue or organ. Electrospun tropoelastin (TE) and collagen scaffolds can be blended to create a cellular delivery device, which can be mechanically adjusted or "tuned". Human adipose-derived stem cells (hADSC), human neonatal fibroblasts (hDFn), and porcine endothelial cells (pEC) were cultured on electrospun scaffolds and evaluated for structural architecture using scanning electron microscopy (SEM). In vitro screening suggests that these scaffolds would support in vivo implantation and cellular delivery.

Tropoelastin is the precursor protein to elastin which is a durable protein found in nearly every organ in the body. The TE used in these studies was manufactured using recombinant techniques and donated by Protein Genomics. The proteins were solubilized and electrospun onto a foil target, creating continuous, solid fibers. This is an ideal process for the production of biomaterial scaffolds with fiber diameters in the submicron range, thus producing a material with physical and spatial properties similar to the topography of the native extracellular matrix of many tissues.

Relative porosity was measured using SEM images of the scaffolds and analyzed computationally (Figure 1). The code was written to threshold the image, eliminate some of the depth of view and measure relative percent porosity based on the amount of black vs. white pixels. These measurements allow for the mimicking of the native extracellular matrix of the target tissue in order to create a more biocompatible material.

The scaffolds were evaluated for stress and strain by using a uniaxial apparatus. The scaffolds were cut into 1cm wide strips with a 1mm gage length and measured under the following conditions: hydrated vs. dry conditions (Figure 2), crosslinked vs. non-crosslinked (Figure 3), and 100% tropoelastin vs. 1:1 tropoelastin/collagen conditions (Figure 4). Hydrated materials were soaked in phosphate buffer for 60

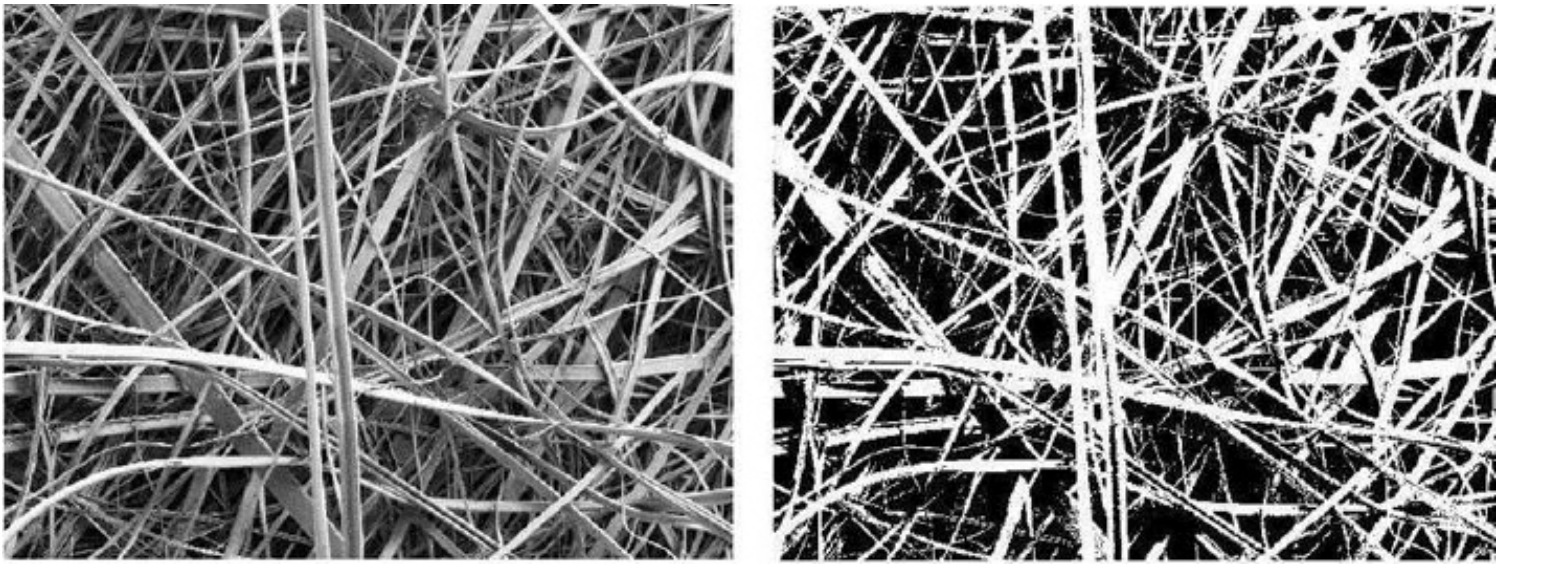

Figure 1. *(Left)* SEM of bare electrospun collagen scaffold, (Right) Threshold image of the scaffold for porosity measurements at 1000x. The black area is summed for a relative percent porosity. This specific example yields a relative porosity value of 54.7%.

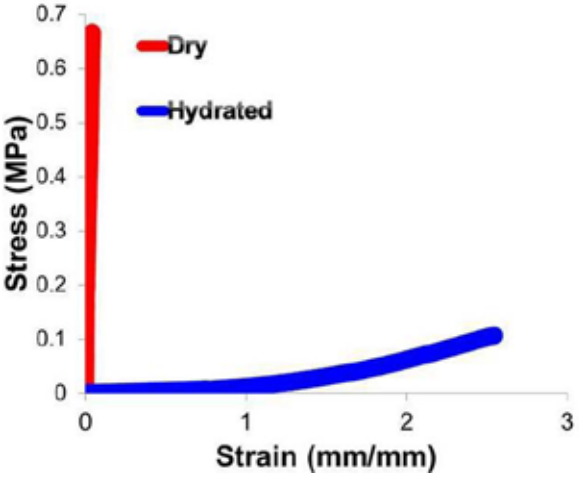

Figure 2. Effect of hydration on tropoelastin scaffold. The hydrated material exhibits a three order of magnitude change in the elastic modulus emphasizing the need to test the materials in an end-use environment.

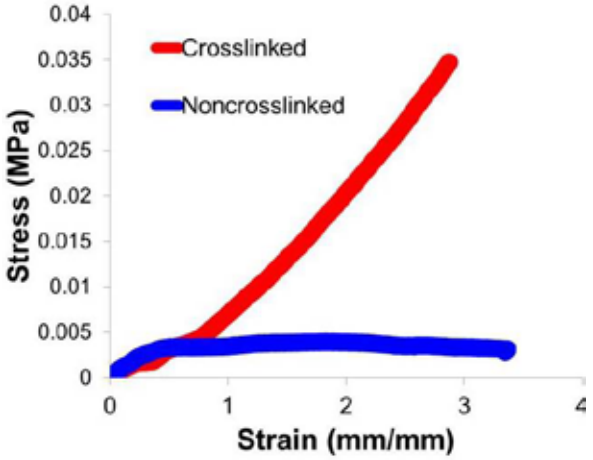

Figure 3. Effect of crosslinking on tropoelastin scaffolds. Crosslinking provides a less compliant material.

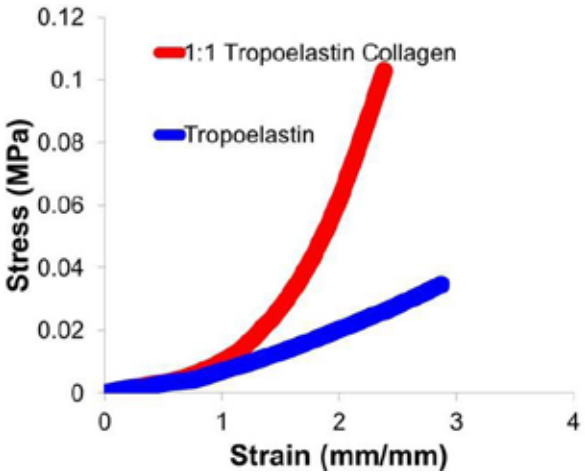

Figure 4. Comparison of crosslinked tropoelastin to 1:1 tropoelastin-collagen blends. Blending the proteins can change the degree of compliance.

seconds prior to and throughout testing. The effect of hydration had a three order of magnitude change in the elastic modulus emphasizing the need to test the materials in an end-use environment. Blending of the scaffolds can yield “tunable” materials which can be used to compliance match various tissues or organs. Tropoelastin may have the flexibility to be used as a resorbable material and the degree of crosslinking may be able to control the half-life of the resorption, as the material showed some mechanical resilience even without crosslinking. Whether in cardiac, dermal, or otherapplications, the tissue scaffolds may be subject to both static and dynamic loads, as they will be attached to the tissues of a dynamic, living organism. As such, the strain-rate dependence of the mechanical characteristics of electrospun tropoelastin and collagen may also be a necessary consideration when designing scaffolds.

For in vitro biocompatibility testing of electro-spun tropoelastin and collagen, human adipose derived stem cells (hADSC) were used to determine if the scaffolds could be used as delivery devices for stem cells into target organs or tissues (Figure 5 & 6). Human dermal fibroblasts (hDFn) were used to represent the use of the scaffolds in a skin environment (Figure 7) and porcine endothelial cells (PEC) were used to determine if the scaffolds could be used in vascular applications (Figure 8). These cell lines were cultured and grown on 2 and 4mm diameter scaffolds.

In conclusion, human recombinant tropoelastin is an elastic biocompatible material with unique mechanical characteristics. Tropoelastin can be blended with other proteins (e.g. collagen) or synthetic materials to create novel scaffolds that offer specific solutions to various tissues. The ability to create “tunable” biocompatible scaffolds will assist in the future development of novel bioengineered solutions for medical challenges.

See Page 11 for figures 5-8

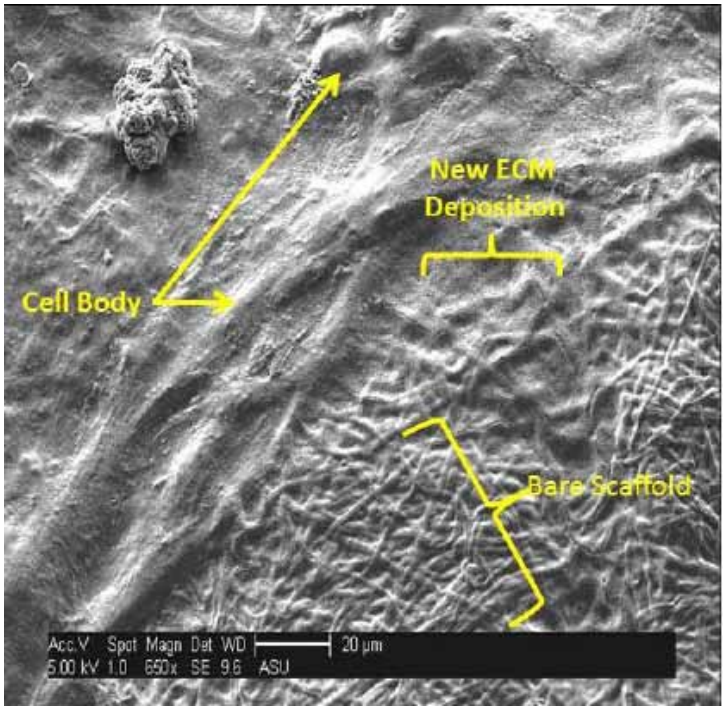

Figure 5. hADSC growing onto 100% tropoelastin scaffold. Large amount of new ECM deposition with typical cellular morphology for hADC.

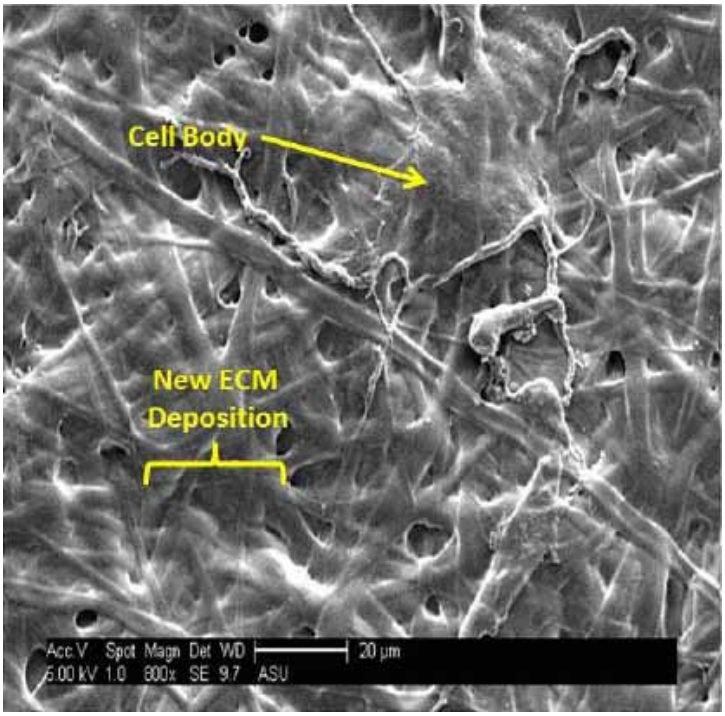

Figure 6. hADSC growing onto 100% collagen scaffold. No bare scaffold in image, the scaffold is covered with new ECM deposition, cells exhibit typical cellular morphology for hADC.

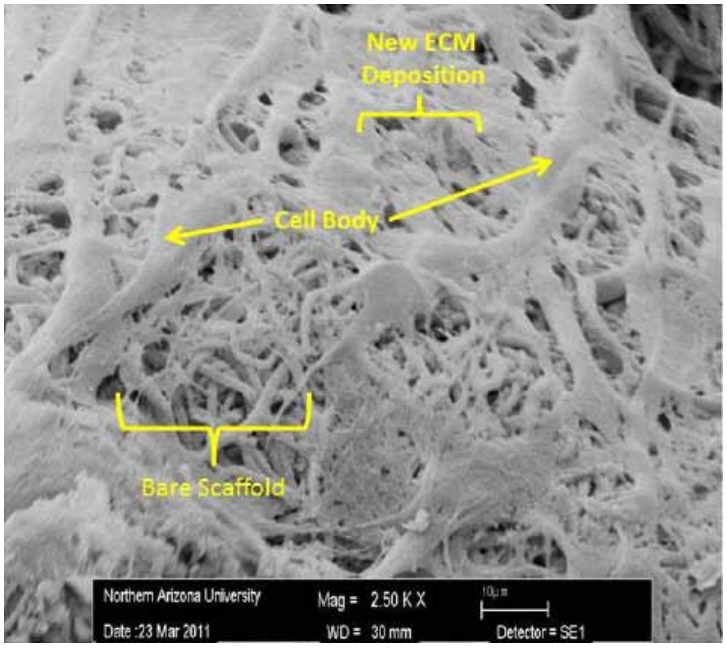

Figure 7. hDFn growing onto 100% tropoelastin scaffold. Large amount of new ECM deposition with normal cel
lular morphology for hDFn.

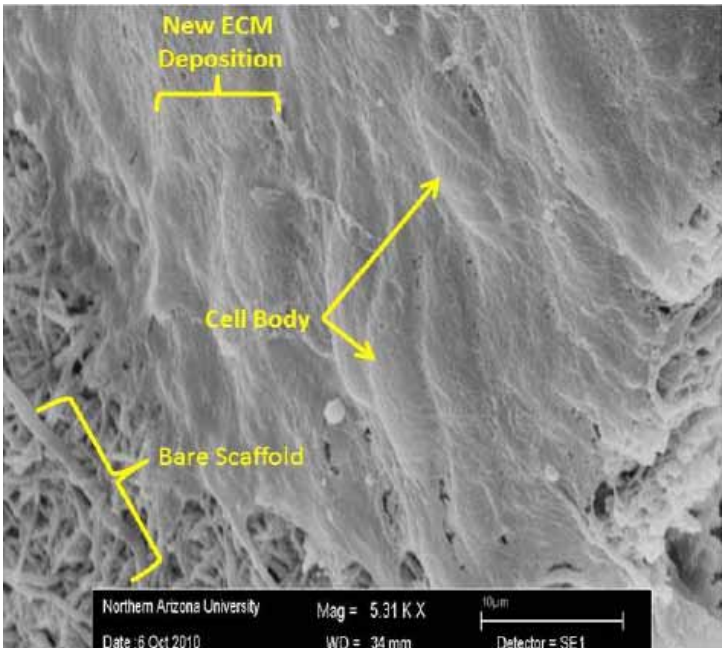

Figure 8. pEC growing onto 100% tropoelastin scaffold. Large amount of new ECM deposition with normal cobblestone morphology for pEC.

Options for FDA Clarification of Device Premarket Submission Requirements

By Phil Triolo PhD, RAC

FDA requirements for marketing a medical product depend on its categorization as a device, drug, biologic, or combination product. For devices, requirements are further identified based on device classification which determines whether a premarket submission is required, and, if so, which type (usually 510k, PMA, or de novo).

Although the FDA provides definitions and guidance documents to assist with identification of premarket submission requirements, the definitions and guidance documents have grey areas and are not always strictly applied. As resource needs are largely dictated by regulatory requirements, the early identification of applicable regulatory requirements is essential.

Manufacturers (including specification developers) have several viable options for obtaining Agency feedback on the categorization of their product and, if it is a device, its classification (Class I, II, II) and premarket application requirements:

Requests for Designation (RFDs) are used to determine if the product is a drug, device, biologic, or combination product; and, if a combination product, the FDA Center with primary jurisdiction over premarket review.

513(g) Requests for Information (513(g)s) are used to classify a device, to determine if a 510k can be submitted, and if so, the suitability of a proposed predicate device. The 513(g) can also be used to help determine the type of information (clinical, non-clinical) that will be required in a premarket submission, and standards and guidance documents that apply.

Pre-Submission Meetings and Materials (Pre-Subs) are used to ask specific questions and obtain FDA feedback on premarket submissions, including IDE's, clinical trial details including Significant Risk (SR) studies, premarket verification and validation test plans, and other issues.

These options are summarized in the following table.

Table 1. Summary of FDA Options for Clarification of Premarket Issues

Option	Cost	Time to respond
Request for Designation	Free of charge	60 days* (by statute)
513(g) Request for Information	$3415 for large, $1707 for small businesses for requests submitted in FDA's 2014 fiscal year	60 days (by statute)
Pre-Submission Meetings	Free of charge	90 days (FDA target**)

*If FDA does not issue a designation letter within 60 calendar days of the filing of the RFD, as required by 21 CFR 3.8(b), the sponsor's recommendation for the classification or assignment of the product will become the designated classification or assignment.

**Recent responses have been provided in as few as 82 days and as many as 330 days.

The major drawback to pursuing one of the options is that the written background materials that need to be provided to the Agency take time to prepare, and there is a delay before a response is received. On the positive side, the process of preparing the materials often results in clarification of your regulatory strategy, device specifications and claims, design verification and validation plans, and clinical investigation protocols; and the documents serve as drafts of, or are controlled documents that need to be created during the design and development of the product to meet design control requirements. In other words, the efforts aren't wasted.

In this first of a 2-Part series, Requests for Designations will be discussed. In the next issue of SurFACTS, information on 513(g) Requests for Information, and Pre-Submission meetings will be presented.

Request for Designation

If you are not sure if your product is a device, drug, biologic, or combination product; or if you know it is a combination product, but you want the FDA to determine which Center (CDER [Center for Drug Evaluation and Research], CBER [Center for Biologics Evaluation and Research], or CDRH [Center for Devices and Radiologic Health]) will have primary jurisdiction over the review of my marketing application; Submit a Request for Designation (RFD).

Relevant Guidance

FDA guidance on RFDs can be found at http://www.fda.gov/RegulatoryInformation/Guidances/ucm126053.htm

Contents of a Request for Designation

According to 21 CFR 3.7(c), you are required to include the following information in your RFD, as applicable.

1. The identity of the sponsor, including company name and address, establishment registration number, company contact person and tele phone number
2. A description of the product, including:

i. Classification, name of the product and all component products, if applicable;
ii. Common, generic, or usual name of the product and all component products;
iii. Proprietary name of the product;
iv. Identification of any component of the product that already has received premarket approval, is marketed as not being subject to premarket approval, or has received an investigational exemption, the identity of the sponsors, and the status of any discussions or agreements between the sponsors regarding the use of this product as a component of a new combination product;
v. Chemical, physical, or biological composition;
vi. Status and brief reports of the results of developmental work, including animal testing;
vii. Description of the manufacturing processes, including the sources of all components;
viii. Proposed use or indications;
ix. Description of all known modes of action, the sponsor's identification of the single mode of action that provides the most important therapeutic action of the product, and the basis for that determination;
x. Schedule and duration of use;
xi. Dose and route of administration of drug or biologic (if applicable);
xii. Description of related products, including the regulatory status of those related products; and
xiii. Any other relevant information.

3. The sponsor's recommendation as to which Agency component should have primary jurisdiction

Section III.E of the FDA's guidance document referenced above further clarifies FDA's recommendations for the information that should be provided.

RFD Decisions

The OCP (Office of Combination Products) was formed to help coordinate activities between a manufacturer and the two or more Centers responsible for regulating combination products. It also responds to RFDs and determines if the subject product is a drug, device, biologic, or combination product on the basis of FDA definitions and other information. The difference between drugs and devices depends on whether the primary intended purposes of the product are achieved through chemical action; and whether or not the product is dependent upon being metabolized for the achievement of its primary intended purposes.

The FDA has defined chemical action in its June 2011 Draft Guidance Document http://www.fda.gov/RegulatoryInformation/Guidances/ucm259059.htm. According to FDA's "current thinking" expressed in the draft guidance document, a product exhibits "chemical action" for purposes of the device definition at section 201(h)

of the FD&C Act if:
Through either chemical reaction or intermolecular forces or both, the product:

- Mediates a bodily response at the cellular or molecular level, or
- Combines with or modifies an entity so as to alter that entity's interaction with the body of man or other animals.

See the draft guidance document. You may be surprised to find how broadly the FDA has defined "chemical action."
OCP also assigns the Center with primary jurisdiction for the review of the premarket documents for combination products on the basis of the primary mode of action of the device.

Primary Mode of Action- 21 CFR 3.2(m) defines "primary mode of action" (PMOA) as "the single mode of action of a combination product that provides the most important therapeutic action of the combination product. The most important therapeutic action is the mode of action expected to make the greatest contribution to the overall intended therapeutic effects of the combination product." As with "mode of action," for purposes of PMOA, "therapeutic" effect or action includes any effect or action of the combination product intended to diagnose, cure, mitigate, treat, or prevent disease, or affect the structure or any function of the body.

Some factors that OCP considers when determining PMOA are provided below. OCP recommends that you consider and address these as appropriate when explaining the PMOA of your combination product:

- The proposed use(s) or indication(s) for the product;
- How it achieves its overall intended therapeutic effect(s);
- The relative contribution of each constituent part to the proposed use(s) or indication(s), and to the overall intended therapeutic effect(s) of the product;
- The duration of the contribution of each constituent part toward the intended therapeutic effect(s) of the product; and
- Any data or information provided by you or that is available in scientific literature that describes and supports the mode of action expected to make the greatest contribution to the overall intended therapeutic effects of the product.

Assignment Algorithm- For some combination products, it may not be possible to determine with reasonable certainty which mode of action of the product provides the most important therapeutic action. In such an instance, 21 CFR 3.7(c)(3) requires the sponsor to recommend which Agency component should have primary jurisdiction based on the assignment algorithm at 21 CFR 3.4(b).

See the guidance document for details. Also be sure to address the items identified in the Appendix: RFD Screening Checklist

Summary
Although it is often difficult to convince management or other members of the product development team to pursue FDA feedback before completing premarket submissions, the pursuit does payoff, typically, in a reduced time to market. The earlier the materials can be prepared and provided to the Agency, the better able you will be to define the appropriate regulatory pathway and eventually market your new devices.

Surface Science Calendar of Events

MD&M West
10 Feb 2014 - 13 Feb 2014
Anaheim, CA USA

Design of Medical Devices Conference University of Minnesota
April 7-10, 2014
http://www.dmd.umn.edu/

Society for Biomaterials
2014 Annual Meeting & Exposition
Pioneering the Future of Biomaterials
April 16-19, 2014
Colorado Convention Center
Denver, CO

2014 IPrime Annual Meeting
May 27-29, 2014
University of Minnesota
Minneapolis East Bank Campus
Minneapolis, MN

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- Promote understanding of interfacial issues common to researchers, bio-medical engineers and material scientists.

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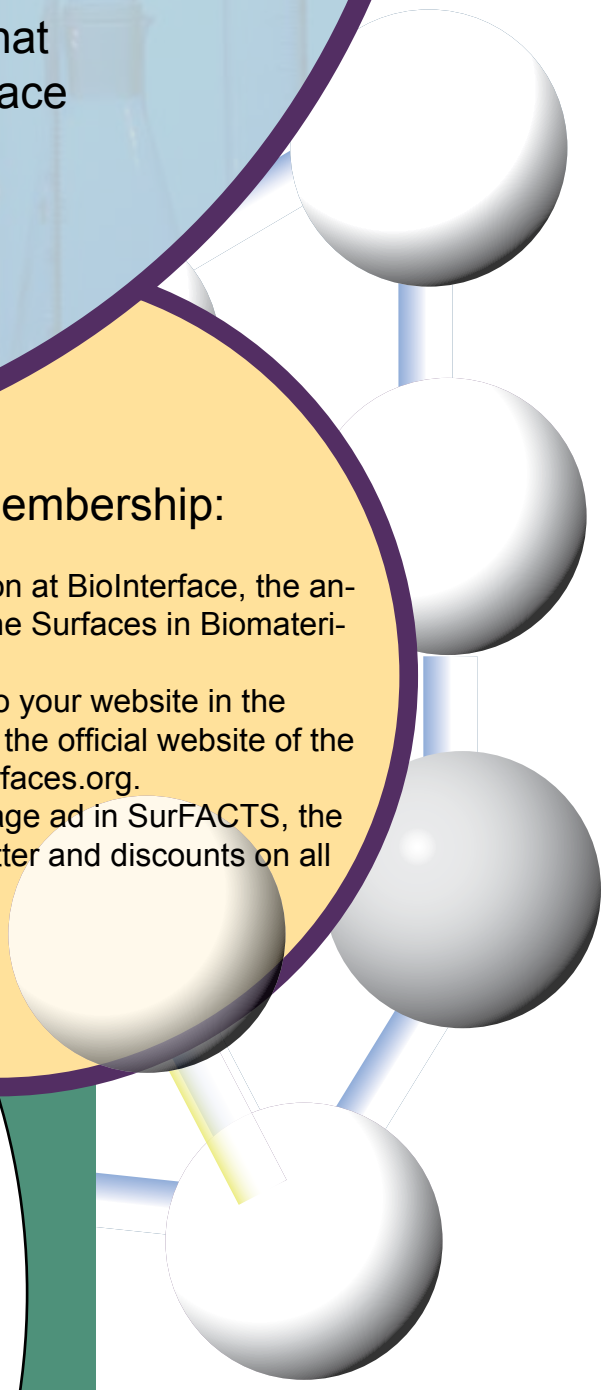
- Complimentary full page ad in SurFACTS, the Foundation's newsletter and discounts on all advertising.



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