

# SurFACTS in *Biomaterials*

Winter 2015

Volume 20, Issue 1

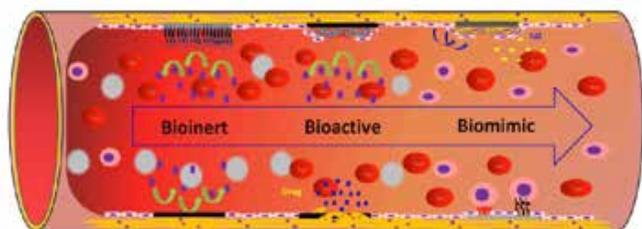
## A Review of Hemocompatible Surface Modification and Coating Strategies for Intravascular Stents

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### INTRODUCTION

Intravascular stents were first introduced in the 1980s and used exclusively to treat coronary and peripheral arterial disease, which are characterized by progressive narrowing of an artery due to the accumulation of fatty lesions.<sup>1</sup> The intravascular stent was designed to enlarge the lumen of the diseased artery, providing permanent mechanical arterial wall support, in addition to serving as a scaffold for healthy endothelial cell growth.<sup>1</sup> Yet these devices are not without complication; approximately 25% of patients treated with intravascular stents experience either recurrent stenosis or late-stage thrombosis and require additional intervention.<sup>2</sup> For the past decade or so, intravascular stents have also been used in the cerebral circulation to support embolization coil placement in the treatment of cerebral aneurysms, which are local dilations of a brain artery; additionally, they have been used to treat cerebral artery atherosclerosis and stenosis.<sup>3, 4</sup> While these cerebral stents differ in function, material composition, and design from their cardiovascular counterparts they still pose risks to the patient, like increased potential for thrombotic embolization and stroke.<sup>3</sup> Likewise, the limitations of the intravascular stent in both the cardiovascular and cerebral circulations has led to the investigation of new stent materials, designs, surface modifications and coatings to mitigate thrombosis-related risks and increase device hemocompatibility. This review outlines the scope of the strategies that have been employed for intravascular stent surface modification and coating as they have progressed from bioinert to bioactive, and ultimately biomimetic (Figure 1).

**A Review of Hemocompatible...** continues on pg. 2



**Figure 1.** The evolution of intravascular stent surface modification and coating strategies (reproduced with permission from Qi et al.<sup>5</sup>).

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Thank you to our members!

### SAVE THE DATE

25th Annual  
BioInterface Workshop &  
Symposium  
September 21–23, 2015  
Fairmont Scottsdale Princess

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# 25th Annual BioInterface Workshop & Symposium

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Scottsdale, Arizona – USA

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Co-Chair: Bill Theilacker, Medtronic, Inc.  
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Chair: Jill Mendelson, Medtronic CardioVascular  
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### Session 2: Chemical and Physical Strategies to Regulate Biological Adhesion

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Co-Chair: Ethan Mann, Sharklet Technologies, Inc.  
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### Session 3: Ophthalmic Drug Delivery

Chair: Sarah van de Graaf, DSM Biomedical Inc.  
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### Session 5: Integration for Tissue Repair and Regeneration

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### Session 6: 3D Printing in Medical Applications

Chair: Chander Chawla, DSM Biomedical Inc.  
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### Session 7: Neuroendovascular

Chair: To Be Announced

### Session 8: Drug Coated Balloons

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## **SURFACE MODIFICATIONS**

Because thrombus formation and embolization are the most substantive risks of intravascular stents, scientists' earliest attempts to improve stent hemocompatibility were to modify the stent surface directly. This choice was made because initiation of the coagulation cascade requires the adsorption of plasma proteins, tissue, and complement factors to the biomaterial surface, the speed of which is governed by surface characteristics. Thus changes in surface composition, morphology, charge, wettability, and roughness elicited by cleaning, polishing, and etching methods can affect protein and factor adsorption.<sup>6</sup> Yet the influence of these surface characteristics on device hemocompatibility remains ambiguous and cannot be generalized across materials.<sup>8</sup> For instance, uncharged hydrophilic surfaces generally promote low surface-blood interaction, yet the highly hydrophobic material of expanded polytetrafluorethylene has been shown to have high hemocompatibility.<sup>8</sup> Thus, it has been difficult for scientists to identify generic surface characteristics that promote hemocompatibility independent of bulk material.

## **PASSIVE INORGANIC COATINGS**

Scientists have also investigated coating intravascular stents with passive inorganic films, the goal of which is to act as an inert barrier between the bulk stent material and the bloodstream or vascular tissue.<sup>1</sup> Notable such coatings are gold, silicon carbon (SiC), diamond-like carbon (DLC), and titanium-nitride-oxide.

Typical deposition techniques for these coatings are plating – for gold – and plasma enhanced chemical vapor deposition (PECVD) for SiC, DLC, and titanium-nitride-oxide deposition.<sup>2</sup> PECVD is a process whereby thin, uniform films can be deposited on a substrate in a vacuum chamber.<sup>2</sup> It works by using electrical energy to generate plasma in a vacuum chamber.<sup>2</sup> The plasma then transfers energy to a mixture of gaseous precursors, transforming them to radicals, ions, and other highly energetic species.<sup>2</sup> Depending upon the interaction of the precursor mixture with the substrate, either etching or deposition occurs on the substrate surface.<sup>2</sup> In this manner thin and conformal films can be deposited at relatively low temperatures.<sup>2</sup>

Gold was initially tested as a passive, inorganic intravascular stent coating because it is a well-known inert material with dental applications.<sup>5</sup> Yet a clinical study called NUGGET, done on commercially available cardiovascular stents coated with gold indicated a recurrent stenosis rate of 37.7%, which was higher than the associated rate for bare metal stents among patients at six-month follow-up.<sup>2</sup> Likewise, SiC was an initially attractive coating to scientists due to its high hardness, chemical inertness, and smooth surface finish on scanning electron microscopy (SEM), yet it is also brittle and may crack.<sup>9</sup> Further, the TENISS and TRUST trials, which were large multicenter trials studying SiC coated cardiovascular stents, indicated no improvement in clinical outcome in patients treated with SiC coated stents compared to bare metal stents.<sup>10</sup> DLC was also an initially attractive coating because it is an inert hydrocarbon<sup>2</sup> that has been shown to exhibit a smooth surface on SEM;<sup>9</sup> yet several large clinical trials have independently concluded that DLC coated cardiovascular stents do not significantly reduce recurrent stenosis rates compared to bare metal stents and therefore are not clinically beneficial.<sup>2</sup> Scientists chose to investigate the hemocompatibility of titanium-nitride-oxide stent coatings because titanium-nitride-oxide is chemically inert and cannot transfer electrons to plasma proteins.<sup>2</sup> Unlike SiC and DLC, titanium-nitride-oxide coating on cardiovascular stents has demonstrated clinical benefits. The TiNOX clinical trial, which compared 45 patients possessing de novo atherosclerotic lesions treated with titanium-nitride-oxide coated stents and 47 patients treated with bare metal stents, found that at 30 days no stent thrombosis had occurred in either group.<sup>2</sup> However, more studies are required to see if this finding can be corroborated.

## **BIOACTIVE COATINGS**

The strategy of bioactive coatings is to immobilize an active pharmacological agent on the intravascular stent surface in order to aid regulation of coagulation, the complement system, or inflammation processes.<sup>5</sup> In other words, bioactive coatings seek to mimic the endothelial cell microenvironment. The earliest attempts at this came in the 1990s and they sought to control the coagulation cascade through the immobilization of heparin.<sup>5</sup> Later researchers investigated the immobilization of direct thrombin inhibitors, in

addition to the immobilization of other anticoagulant molecules like thrombomodulin (TM) and nitric oxide (NO).<sup>5</sup> Nevertheless, the heparin bioactive coating is the oldest and most widely used on intravascular stents.<sup>5</sup> Initially discovered in 1961 as an anticoagulant drug, heparin was later found to interact with antithrombin, which accelerates the binding of thrombin and inhibits amplification of the coagulation cascade.<sup>5</sup> The heparin coating strategies range from physical adsorption to covalent side-on or end-on immobilization.<sup>5</sup> Direct thrombin inhibitors have also been investigated, as they are anticoagulant molecules that directly block thrombin active sites and therefore inhibit coagulation.<sup>5</sup> Hirudin, naturally derived from snake venom, is one such thrombin inhibitor that has successfully been covalently immobilized to create a surface with anticoagulant properties.<sup>11</sup> Other synthetic thrombin inhibitors like D-Phe-Pro-Arg-chloromethylketone<sup>12</sup> and an amidine derivative<sup>13</sup> have been covalently immobilized to foreign surfaces with positive anticoagulant and anti-inflammatory effects. Additionally researchers have tried inhibiting the coagulation cascade via other anticoagulant molecules like TM and NO. Particularly TM functions as an endothelial cell surface glycoprotein promoting protein C activation, which in turn acts as an anticoagulant.<sup>14</sup> Akashi et al.<sup>15</sup> reported the successful immobilization of TM on a foreign surface in 1992 and, since then, TM has been immobilized by other researchers.<sup>16</sup> NO has been shown to be a modulator of vascular tone and permeability, in addition to inhibiting leukocyte adhesion and platelet activation.<sup>5</sup> Likewise several research groups have reported both NO-eluting and NO-generating coating designs on polymer and metal substrates with promising results.<sup>17, 18</sup> Yet two primary challenges exist for all bioactive coatings: 1) properly orienting the pharmacologic agent within the coating and 2) protection of the pharmacologic agent from physiological degradation process. Likewise, how to sterilize such coated materials and their limited shelf stability are technical challenges.<sup>8</sup>

## MICRO-AND NANO-STRUCTURED SURFACE

Recent advances in both micro- and nanotechnology have enabled researchers to modify intravascular stent surface characteristics on the micro and nano-scales in order to promote endothelial cell adhesion and proliferation, as well as inhibit the adhesion of platelets and plasma proteins.<sup>1</sup> The interest in this

area has grown because it has been hypothesized that endothelial cells grow in-vivo on a micro- and nano-patterned basement membrane; thus, the potential for biomimicry has fueled interest.<sup>1</sup> While 2D micro- and nano-structured features have been created using many fabrication techniques – photolithography, focused-ion-beam lithography, nanoimprint lithography, physical vapor deposition, chemical etching, among others – integrating these small-scale features onto 3D biomaterials remains a challenge.<sup>1</sup> Additionally the mechanisms underlying the interactions between vascular cells and the structured surface are not yet well understood.<sup>1</sup> Future investigations should continue to study how feature dimension and geometry affect the adhesion, proliferation, and migration of vascular cells.<sup>1</sup>

## SUMMARY

To mitigate thrombosis-related risks and increase intravascular stent hemocompatibility, researchers have investigated and employed various stent surface modifications and coatings ranging from bioinert, to bioactive, and biomimetic. These strategies are summarized in Table 1. While attempts to change the macro stent surface characteristics have been inconclusive, the titanium-nitride-oxide coating remains the most promising passive, inorganic coating. Bioactive coatings are also promising; however more work needs to be done to address the limitations. An alternate strategy is to create a micro- and nano-structured stent surface that mimics the in-vivo basement membrane. This could even be combined with current bioactive coatings, though further studies are needed to elucidate the mechanisms driving the interaction between vascular cells and the structured surface.

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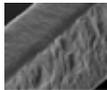
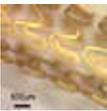
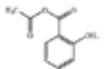
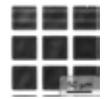
	Modification or Coating	Merits	Demerits	References
	Surface Modification	<ol style="list-style-type: none"> <li>1. Relatively easy to create</li> <li>2. Durable</li> <li>3. Sterilizable</li> </ol>	<ol style="list-style-type: none"> <li>1. Influence on hemocompatibility is difficult to generalize</li> </ol>	Werner et al. <sup>8</sup>
	Passive Inorganic Coating	<ol style="list-style-type: none"> <li>1. Created via common film and coating deposition techniques</li> <li>2. Sterilizable</li> </ol>	<ol style="list-style-type: none"> <li>1. Long-term hemocompatibility results have lacked promise</li> </ol>	Nazneen et al. <sup>1</sup> Sydow-Plum et al. <sup>2</sup>
	Bioactive Coating	<ol style="list-style-type: none"> <li>1. More closely mimics endothelial cell micro-environment</li> </ol>	<ol style="list-style-type: none"> <li>1. Prone to degradation; limited stability</li> <li>2. Difficult to orient active agent to maintain functionality</li> <li>3. Difficult to sterilize</li> </ol>	Qi et al. <sup>5</sup> Werner et al. <sup>8</sup>
	Micro- and Nano-Structured Surface	<ol style="list-style-type: none"> <li>1. Most closely mimics endothelial cell micro-environment</li> </ol>	<ol style="list-style-type: none"> <li>1. Interactions between structured surface and vascular cells are poorly understood</li> </ol>	Nazneen et al. <sup>1</sup>

Table 1: Summary of Intravascular Stent Surface Modification and Coating Strategies.

## Member News

**Peter Edelman** of **Boston Scientific** was elected as a fellow in the American Institute for Medical and Biological Engineering (AIMBE). Peter is a past president of the SIBF and we congratulate him on receiving this honor. Boston Scientific also announced results from a clinical trial of the SYNERGY™ bio-absorbable coronary stent. The stent demonstrated non-inferiority in terms of target lesion failure and low rates of thrombosis. The company also received FDA and CE Mark approval for the CoverEdge™ surgical leads for use in pain treatment with a spinal cord stimulator.

The National ESCA and Surface Analysis Center for Biomedical Problems (**NESAC/BIO**) at the **University of Washington** has received an additional five years of funding from the NIH. NESAC/BIO has projects in technology research and development (TRD), collaboration research, service, training and dissemination. The major TRD thrusts for the coming five years are:

- development of time-of-flight secondary ion mass spectrometry (ToF-SIMS) methods for imaging
- sputter depth profiling and 3D analysis of complex organic materials, cells and biological tissues

- characterization of the surface composition and structure of nanoparticles with electron spectroscopy for chemical analysis (ESCA) and sum frequency generation (SFG) scattering and vibrational spectroscopy
- developing multi-technique approaches for characterizing the structure and interactions of biomolecules with interfaces.

In the coming months the following new tools will be added to the NESAC/BIO tool set: a Q-Sense quartz crystal microbalance with dissipation (QCM-D), an Insplorion Xnano and an Ionoptika J105 Chemical Imager funded by a grant from the NIH High End Instrumentation Program.

**Gore** received CE Mark approval for its GORE® VIABAHN® Endoprosthesis for the treatment of obstructed peripheral veins in hemodialysis patients. The device is coated with the Carmeda heparin coating to provide thromboresistance and intended for revisions in dialysis access.

**Medtronic** received FDA approval for its IN.PACT Admiral drug coated balloon for the treatment of peripheral artery disease. The balloon, which delivers paclitaxel, showed improved patency as compared to angioplasty with standard balloons in clinical trials. The company also announced the start of a clinical trial to evaluate the effectiveness of the TYRX™ absorbable antibacterial envelope in reducing infections in patients with cardiac implantable electronic devices. Medtronic also launched the NovaShield™ injectable nasal packing and stent for functional endoscopic sinus surgery. The device is made from chitosan and prevents bleeding and adhesions and avoids the painful removal of non-degradable packing materials. The device also has innate antibacterial activity due to the use of chitosan. Medtronic also received regulatory clearances required for its impending acquisition of Covidien.

**Corline Systems** was granted a Canadian patent for the use of its heparin coating technology on biological tissues for regenerative medicine. They also received a grant from the Swedish government to study the use of the heparin coating to enhance the performance of islet cell transplantation. The goal is for the coating to reduce the number of islet cell donors required to treat patients with type 1 diabetes.

**Saint Jude Medical** received FDA approval of the TactiCath Quartz Contact Force ablation catheter for treatment of atrial fibrillation. The device provides real-time force measurements to physicians to provide greater control during ablation procedures. The company also released results from the CHAMPION trial looking at patient outcomes with pulmonary artery pressure monitoring using the CardioMEMS™ HF system. Monitoring and treatment with the system reduced hospital readmission compared to the standard of care. Saint Jude also announced the start of a clinical trial of its FlexAbility™ Ablation Catheter System which combines ablation with an implanted defibrillator for treatment of ventricular tachycardia. The STAR-VT trial will compare ablation with defibrillator implantation against the use of defibrillators alone.

**DSM Biomedical** announced positive clinical results with an adhesion barrier device developed by Actamax Surgical Materials. Actamax is a joint venture of DSM and Dupont and has developed a sprayable device to prevent surgical adhesions. DSM also will be partnering with Groupe Sebbing to distribute its Meso BioMatrix™ peritoneal surgical material.

**ExThera Medical** published results in PLOS ONE on the use of its affinity blood filter to treat infections with “CRE Superbugs”. The study showed that the device could remove the bacteria from spiked blood samples and offers promise for the use of the device to treat patients with antibiotic resistant infections. The company also joined a team led by Battelle to develop a device to treat sepsis.

**Covidien** received CE Mark approval for its Stellar-ex™ drug coated balloon. The balloon platform was sold to Spectranetics for \$30 million as required by the FTC to approve the sale of Covidien to Medtronic. Covidien also received 510(K) clearance for the HawkOne™ atherectomy system for treatment of peripheral artery disease and the Fortrex™ PTA balloon. The HawkOne device expands the company's portfolio of atherectomy devices and uses an enhanced cutting mechanism. The Fortrex balloon provides higher pressure inflation for use in opening access for hemodialysis. The company also published results from the MR CLEAN trial demonstrating a clinical benefit in the treatment of stroke with the use of the Solitaire™ thrombectomy device.

# Lubricity and Durability Evaluation of Medical Device Surfaces

Gang Pu, Ryan Farel, June Li, Dehua Yang — Ebatco, Eden Prairie, MN

## Abstract

Biotribology is a key to understanding surface related phenomena and is critically important in a number of biomedical applications such as coating, adhesion and lubrication. In this paper, we will discuss the concept and importance of biotribology study and its experimental techniques. Several examples of biotribology analysis are presented to highlight its useful applications.

**Keywords:** friction, lubricity, wear, medical devices

## Introduction

Many medical devices undergo constant contact with the human body as well as with other device components. Lubricity and durability play critical roles in the functionality and safety of these devices. For example, intravascular balloon catheter systems require their surfaces to have a low coefficient of friction in order for the catheters to easily slip through tortuous vasculature to its destination.<sup>1</sup> Reduction in contact lens lubricity and increase in friction would cause discomfort and dryness for users at the end of a day.<sup>2</sup> Wear particles from the implant medical device surfaces may cause serious adverse health consequences or even death. For instance, the coating of the guide wires used to facilitate percutaneous coronary interventions could detach and cause clots, which may lead to a stroke or heart attack.<sup>3</sup> When wear particles are small enough, even if their bulk formats are considered biocompatible, they would trigger an inflammatory response and cause failure of the entire devices.<sup>4</sup> Therefore, a better understanding on tribology of bio-systems will be helpful for improvement in designs of medical devices.

Due to its importance and challenges, biotribology has received considerable attention in the medical device industry as well as in academics recently. Biotribology specifically focuses on the interactions of friction, wear, and lubrication in biological systems. Friction is the force resisting relative motion between two contact parts. Wear is erosion or detachment process of materials from a surface in motion while in contact with another surface. Lubrication is the reduction in friction through a third body that separates two solid surfaces in relative motion. These three subjects are interlocked and influenced one another. The possible relationship

Lubricity and Durability... continues on pg. 8

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among them is still not yet fully understood. In general, wear can be reduced by lubrication, and the separation of the solid surfaces by lubricant will also reduce friction. The mechanisms of friction and wear for hard surfaces, such as metals and ceramics, have been well studied in the last several decades. However, the interactions between soft surfaces, which are common in biological systems, are still a challenging area. The soft surfaces usually have complex viscoelastic responses which strongly depend on the loading frequency, temperature and material properties such as the glass transition temperature. The possible swelling caused by lubricants can make this situation much worse.

One of the most commonly used instruments for tribology testing is a tribometer. A reciprocating tribometer applies a reciprocating load to a sample surface and the friction is recorded during sample's relative motion. The static and kinetic friction coefficients can be measured in a single pass over a sample surface with a specific contact part under a controlled load, speed and temperature setting. The lubrication could also be evaluated using a tribometer by immersion of the sample and the contact part within lubricants. The wear test is carried out on a tribometer by allowing the samples to slide for specified multiple cycles and the material to be removed from the wear track. The wear track produced from the reciprocating rubbing can be analyzed through optical profilometry or scanning probe microscopy to estimate the wear volume. The wear debris could also be collected for particle size and compositional analysis. Recently, tribological studies have trended towards using advanced modeling and testing in micro and nano scales.

In this paper, authors will provide several examples of biotribology studies performed in our Nano-Analytical Lab in Eden Prairie, MN. The tests were performed on a Kyowa TS-501 Tribometer and scanning probe microscopy on a Hysitron TribolIndenter system. The experimental results and significance of each study will be discussed. Authors hope to help readers to get

familiar with biotribology techniques and to gain a better understanding on tribological phenomena and applications.

### Friction of Contact Lenses

Most of the disposable contact lenses are made of extremely soft hydrogels with a significant amount of water content. Wearing contact lenses is becoming trendy for people whether it is for cosmetic, corrective or therapeutic reasons. In addition to many designed functionalities of the contact lenses, wearing comfort is a key factor to be considered by the contact lens designer. One of the aspects of the wearing comfort is the friction between eyelid and the contact lens.

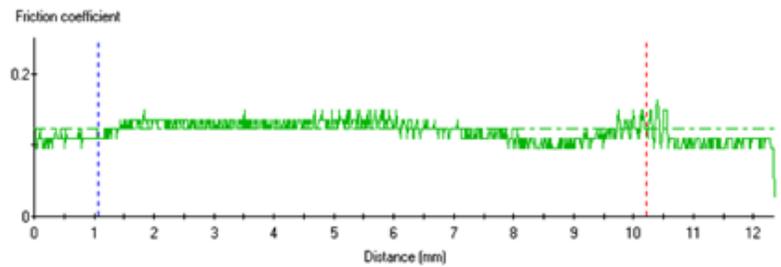


Figure 1. Friction coefficient as a function of sliding distance for the 1-Day Acuvue TruEye contact lens against glass slide in saline contact lens solution.

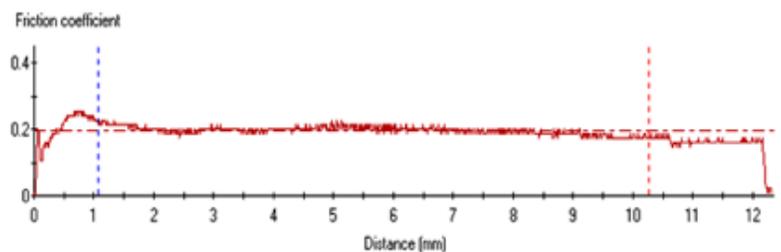


Figure 2. Friction coefficient as a function of sliding distance for the Acuvue Oaysis with Hydraclear Plus contact lens against glass slide in saline contact lens solution.

Friction Coefficient	1-Day Acuvue TruEye	Acuvue Oaysis with Hydraclear Plus
$\mu_s$	0.123	0.255
$\mu_k$	0.123	0.195

Table 1 Static and Kinetic Friction Coefficients of Contact Lens Sliding against Glass Slide in Saline Contact Lens Solutions

As shown in Figures 1 and 2, and Table 1, two different kinds of commercially available contact lenses from Johnson & Johnson Vision Care, Inc. were tested for friction using the reciprocating tribometer TS-501. The first kind of contact lens tested was 1-Day Acuvue TruEye disposable contact lens. The second kind of contact lens

was Acuvue Oaysis Hydraclear Plus disposable contact lens. Both kinds of contact lenses were tested under the same conditions and parameters sliding against glass slide in saline contact lens solution. From the results, it is apparent that the static and kinetic friction coefficients for the two kinds of contact lenses are different. The different friction coefficients would result in different wearing comfort for the users.

does not have inflammatory response or loss of cell integrity. This character makes DLC film an excellent candidate for biomedical applications. DLC films can be produced by a number of deposition techniques such as ion beam deposition, radio frequency plasma enhanced chemical vapor deposition, magnetron sputtering, ion beam sputtering, pulsed lased deposition and mass selected ion beam deposition, etc.

**Wear of DLC Coating**

Diamond-like carbon (DLC) is a class of amorphous carbon materials that has been widely used as coating materials in medical device industry in recent years due to many of its superior mechanical properties such as high hardness, low frictional coefficient, high wear and corrosion resistance.<sup>5</sup> Especially, DLC film has a good biocompatibility; the studies show that DLC coating

The data presented here are for an ultrathin DLC coating that underwent reciprocating wear tests. After the wear tests, three segments from each wear track were analyzed using scanning probe microscopy in order to determine the cross-sectional area of the wear tracks as shown in Figures 3 and 4. From the cross sectional area and the stroke length, the wear volumes were determined as shown in Table 2. Knowing the wear volume,

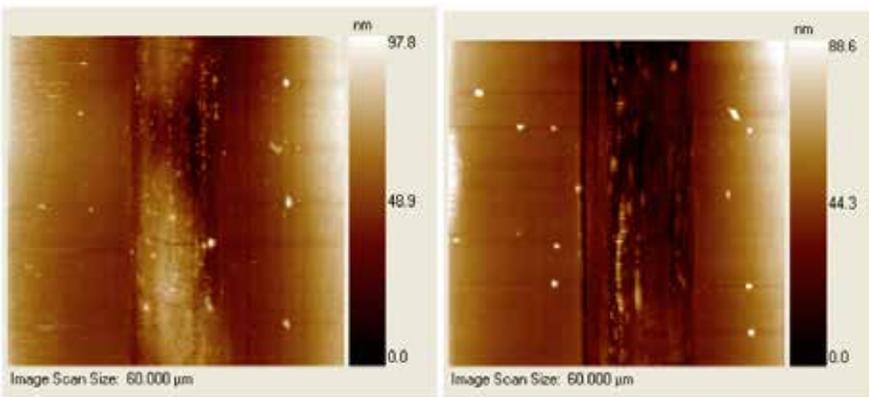


Figure 3. Scanning probe microscopy images of the 700 cycle (left) and 1000 cycle (right) wear tracks on a DLC coating surface.

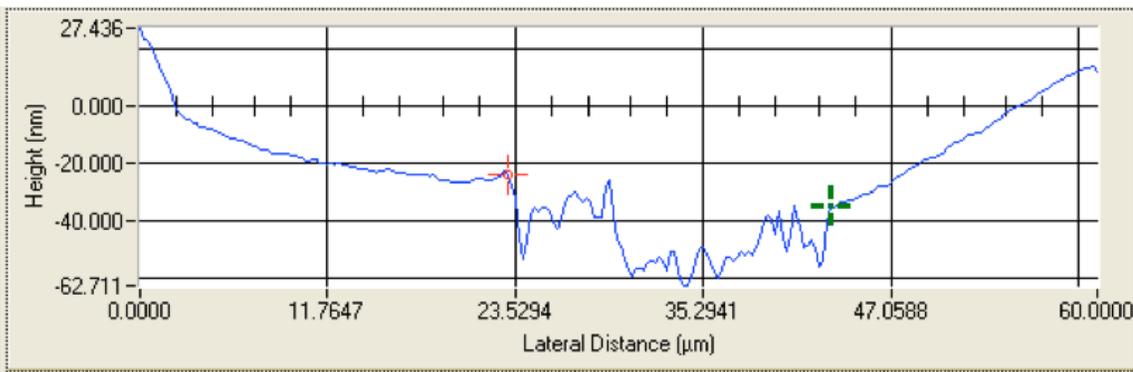


Figure 4. Line profile across the 1000 cycle wear track on a DLC coating surface.

Test Cycles	Wear Cross Section 1 (μm <sup>2</sup> )	Wear Cross Section 2 (μm <sup>2</sup> )	Wear Cross Section 3 (μm <sup>2</sup> )	Average (μm <sup>2</sup> )	Wear Volume (μm <sup>3</sup> )	Wear Rate (m <sup>3</sup> /N*m)
700	0.335	0.397	0.216	0.316	3160	2.30*10 <sup>-15</sup>
1000	0.531	0.47	0.323	0.441	4410	2.25*10 <sup>-15</sup>

Table 2 Wear Test Results of a DLC Coating

force and total sliding distance yields, the wear rate of the DLC coating under the selected wear testing conditions.

As exemplified above, light load, high speed reciprocating wear analysis is a very useful and effective approach to evaluate wear resistance and durability of ultrathin films, coatings and bulk material surfaces used in applications where contact force is low and sliding speed is high.

### Friction Coefficient of Catheter

A catheter is a thin and flexible tube made of silicone rubber, polyurethane, polyethylene terephthalate latex or thermoplastic elastomers. Catheters work as a conduit to deliver fluids or gases into or out of the human body. Sometimes a catheter is pushed through the small blood vessel or tortuous vasculature to reach its target location. The friction forces applied by a catheter on the blood vessel wall can induce vasoconstriction and injury. Research has been focused on reducing the friction between the catheter and vessel to reduce the work and damage caused by the insertion process. New low-friction materials or coatings are applied for such applications. Theoretical models were developed and clinical trials were performed to describe the complex friction between catheters and blood vessels. The aspects modeled and studied include the contact angle between the catheter and the blood vessel wall, the viscoelastic response of both surfaces and the deformation of the vessel walls.<sup>1</sup> The recent development in catheter robots also needs precision control of friction feedback in order for them to safely interact with and repair fast moving cardiac tissue.<sup>6</sup>

Friction Coefficient	0.2 mm/s	1 mm/s	5 mm/s	20 mm/s
μs	0.141	0.211	0.508	0.526
μk	0.095	0.142	0.149	0.159

Table 3 Static and Kinetic Friction Coefficients of Stainless Steel Ball Sliding against Inside Surface of Catheter at Different Sliding Speeds

Friction Coefficient	23 °C	37 °C
μs	6.013	4.488
μk	3.935	3.487

Table 4 Static and Kinetic Friction Coefficients of Silicone Block Sliding against Outside Surface of Catheter at Different Temperatures at 0.2 mm/s Sliding Speed

Following are the experimental results on friction coefficient of catheters under different testing conditions. Table 3 contains the friction coefficients between the inside surface of one catheter and a stainless steel ball at different sliding speeds. Table 4 contains the friction coefficients between a silicone block (simulating a human body tissue) and outer surface of a catheter tube at room temperature (23 °C) and human body temperature (37 °C). From Table 3, it can be known that the friction coefficients increased with sliding speed, especially the static friction coefficient increased by about 370%. From Table 4, it can be seen that the friction coefficients between silicone block and the catheter outer surface decreased with the increase in temperature.

### Summary

Tribology plays a critical role in medical device applications. The fundamentals of tribology research involve mechanical, physical and chemical phenomena at interfaces. The main concepts, techniques and applications of tribology analysis for medical applications are presented in this paper. Exemplary applications of biotribology i.e. friction of contact lens, wear test of DLC coating and friction of catheters were provided. The authors hope this brief introduction and overview paper could be useful for the scientists and engineers who are working with friction, wear and lubricity analysis of medical devices.

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# Update on Important 510(k) Guidance Documents issued by the FDA in 2014

Phil Triolo, PhD, RAC

In 2014 the FDA published several guidance documents on 510(k)s. One of these, *Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications [510(k)] with Different Technological Characteristics: Draft Guidance for Industry and Food and Drug Administration Staff*, <http://www.fda.gov/RegulatoryInformation/Guidances/ucm282958.htm> was issued on July 15, 2014. This draft guidance, if it becomes final, would spell trouble for clearance of 510(k)s submitted in the future, as it documents a need for “valid scientific evidence” in notifications when a new device has the same intended use as a predicate device but has different technological characteristics which do not raise different issues of safety and efficacy of the predicate device. Specifically, the problematic text appears in Section B. Performance Data:

“When FDA is reviewing a new device that has different technological characteristics than the predicate device, performance data may be necessary to assess the safety and effectiveness of the new device as compared to the predicate device.<sup>7</sup> When evaluating the performance data, FDA may consider the risks and benefits of the new device in comparison to the predicate device before making a substantial equivalence determination. The type and quantity of performance data that may be necessary to support a determination of substantial equivalence depends upon the new device. Performance data may be generated from both non-clinical and clinical testing, and both non-clinical and clinical data can play a role in FDA’s evaluation of benefits and risks. Both types of performance data can provide information relating to the benefit and risk factors discussed in this guidance.

“FDA relies on valid scientific evidence when evaluating benefits and risks, including when identifying “probable risks” and “probable benefits.” In general, a “probable risk” and a “probable benefit” do not include purely theoretical risks and benefits, but rather are supported by valid scientific evidence. Generally, isolated case

reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show the new device’s safety or effectiveness in comparison to a predicate device. However, such information may be considered when identifying a device that has questionable safety and effectiveness.”

“Valid scientific evidence” is defined in 21 CFR 860.7(c)(2) as “evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use.” Or, in other words, if your new device has different technological characteristics than the predicate device and performance data are necessary to assess safety and efficacy (and they always are), FDA relies on “valid scientific evidence” when evaluating benefits and risks. Data from the evaluation of the device in humans that constitute “valid scientific evidence” will be relied on to inform a decision on clearance of the device.

The comment period on this guidance has expired, but you can still send comments to <http://www.regulations.gov> citing Agency/Docket Number: Docket No. FDA-2014-D-0900 Document Number: 2014-16565. You may wish to express your concerns with the need for “valid scientific evidence” to inform benefit/risk decisions in 510(k)s.

Another final guidance, *The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)] Guidance for Industry and Food and Drug Administration Staff* <http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm404770.htm> issued on July 28, 2014 is more encouraging,

Update on Important 510(k)... continues on pg.12

especially to the Surfaces community. The document updates and clarifies the Agency's decision-making process for determining substantial equivalence. It is certainly worthwhile taking a careful look at this document if you haven't already done so, as it provides a new 510(k) Decision-Making Flowchart in Appendix A. The FDA notes that the Flowchart is meant to be used in conjunction with its guidance document and not as a "stand-alone" document without appropriate references to the context of each critical decision point, as well as the FDA's current thinking.

The portion of this guidance that is potentially most useful to the Surfaces community appears on page 13; where the FDA explains how the information used for a coating that is applied to a cleared hip implant may be leveraged in a pre-market notification for an implant with the same coating intended for use as a knee implant. The manufacturer "may refer to the reference device (the hip implant with coating X in this situation) to support the appropriate scientific methods for the characterization of coating X on the new knee implant device. In this particular example, the manufacturer provided an adequate scientific rationale to support that the methods used to characterize the biocompatibility and characteristics of the coating (e.g., strength, abrasion, etc.) on the hip implant are applicable to the knee implant.<sup>17</sup> The reference device (hip implant with coating X) is used in this case solely to assist with the characterization of the coating on the new device (knee implant with coating X)."

The FDA accepts that the same test methods used to characterize the coating for the hip device may be used to assess the coating on the new knee device, and that the 510(k) for the hip device may be cited as a "reference" predicate device. It

may also be possible to use some of the data collected for the safety and performance of the hip coating in the 510(k) for the knee, depending on the conditions of the test and the relevance of the test conditions and acceptance criteria for the hip implant to the knee implant.

The Agency cautions in its footnote 17 that "The applicability of the scientific methodology used to characterize certain aspects of a legally marketed device will depend upon the specific scenario. In this example, it is determined that the duration of contact, which affects the biocompatibility testing, and the mechanical testing conducted to fully characterize the coating on the hip implant are directly relevant and informative for the same coating applied to the knee implant. However, if the manufacturer wanted to rely on the scientific methodology for a coating used in a different type of implant (e.g., cardiovascular), it may not be appropriate to exercise this approach." Fair enough.

The Agency has promised to publish an additional 25 guidance documents in 2015 at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MDUFAIII/ucm321367.htm>. Notable on the list are promised guidance documents on 510(k) Submissions for Medical Devices that Include Antimicrobial Agents and on Coronary Drug Eluting Stents-Nonclinical and Clinical Studies, with plenty of others addressing everything from 3D Printing to small bore connectors and laboratory developed tests. The important requirements of the guidance documents relevant to the Surfaces community will be addressed in future articles to appear in this column.

## Patent Trolls – Avoiding A Trolling Embrace

Colin L. Fairman©, Christensen Fonder, PA

There has been a lot of talk recently about “Patent Trolls” and though the name sounds ominous, this column attempts to provide a more clear discussion of what is really meant by “patent troll”, how to avoid their embrace and how to know when to pay up.

Patent trolls may also be more sympathetically referred to as “patent assertion entity” (PAE), a “patent holding company” (PHC) and as a “non-practicing entity” (NPE). As the last moniker suggests, patent trolls are persons or entities that enforce patents against purported infringers but who neither make the products nor use the services that are protected by the patent.

Generally, patent trolls seek out patents or patent portfolios that are for sale due to bankruptcy or divestment. In most cases, this allows patent trolls to gain large chunks of IP for very small prices but also to concentrate in a single technology which may have been identified beforehand as a particularly rich technology area for the trolls.

The modus operandi for patent trolls is to identify a patent that may cover an arguable seminal development in a technology. Currently, the “hot” technologies for patent trolls are LED lighting, power generation and computer/cell phone technologies. The patent troll may then identify some part of one of its patents that covers that technology. For example, one troll “MPHJ Technology” (MPHJ) claims to own patents that cover any networked “scan-to-email” function. MPHJ sent demand letters to over 1,465 small businesses demanding a \$1000 licensee fee per employee or sign a document swearing not to use the technology. MPHJ is now using the threat of its demand letters to consumers to pressure scanner companies to pay an up-front fee to leave the consumers alone. MPHJ acquired its patents for one dollar.

As is generally the case with patent trolls, their initial focus is on smaller firms that may have some

resources but neither in-house legal staff nor a dedicated attorney. Thus, as in MPHJ’s case, an initial 16,000 demand letters were targeted to firms identified as having from between 20 and 100 employees. The first letter lists the patents and states that MPHJ believes the company is largely infringing them. A second letter was sent on the letterhead and provided a phone number to call for more information. However, the phone number was not that of the law firm but of a call center working on behalf of MPHJ. A third letter was sent together with a draft complaint along with a letter from the law firm stating that failure to take a license would result in the suit being filed. In all, beginning with 16,000 demand letters, MPHJ managed to sell 17 licenses.

So, how did the other 16,000+ recipients of the demand letter manage to avoid paying the license fee? They simply did not respond to the demand letter. In this context, it is important to note that ignoring a demand letter is not the same as not responding to it. On the contrary, it is important that the recipient of such letters undertake some exercise to identify whether their actions may or may not infringe the asserted patent. Obtaining a freedom to operate or non-infringement opinion is one such exercise and armed with a valid opinion, an assertion of “willful” infringement can be avoided should the troll continue its attempts to extract a license from the supposed infringer. Further, in litigation, should the patent holder gain a judgment against the asserted infringer – after service of a cease and desist letter, for which the asserted infringer has not received a bona fide opinion of counsel, “willful” infringement means that the infringer may receive a judgment of treble damages and payment of the patent holder’s legal bills. While patent litigation or coercion to a license can be enormously expensive, willful infringement is much more so.

**Patent Troll - Avoiding a Trolling...** continues on pg.14

BIGGEST PATENT TROLLS <sup>1</sup>	
ENTITY	DESCRIPTION
Acacia Technologies	<ul style="list-style-type: none"> <li>• 1757 U.S. Patent Publications; 755 Patent Families; 319 Litigations</li> <li>• Inventors and patent owners hire Acacia to license their IP to corporations</li> <li>• Patent owners split the licensing revenue with Acacia</li> <li>• Licensees: Sony, Exxon, Microsoft, and other huge companies</li> </ul>
ArrivaalStar	<ul style="list-style-type: none"> <li>• Most litigious patent troll</li> <li>• Filed 137 new infringement suits over its vehicle-tracking patents</li> <li>• Make no products; patent monetization entity</li> <li>• Asserts patents against major automakers and transit agencies</li> </ul>
Commonwealth Scientific and Industrial Research Organization	<ul style="list-style-type: none"> <li>• 804 U.S. Patent Publications; 591 Patent Families; 12 Litigations</li> <li>• Public institution (or licensing arm) focused primarily on research and education</li> <li>• LED industry sectors: Power Management, LED control and Epitaxy</li> </ul>
Innovatio IP Ventures LLP	<ul style="list-style-type: none"> <li>• Targets those who provide access to Wi-Fi networks in public spaces like coffee shops and hotels</li> <li>• Purchased patents from Broadcom</li> <li>• Demanded \$2500 per location</li> <li>• Cisco router manufacturer settled with Innovatio for 3.2 cents a unit but spent \$13 million on legal fees</li> <li>• Sues end-users, not manufacturers</li> <li>• Some of the people sued were already protected by a license retained by Broadcom but were not told and did not realize</li> <li>• Patents were subject to a FRAND royalty of 9.56 cents per device</li> <li>• Innovative Wireless Solutions, LLC is a copycat troll of Innovation</li> </ul>
Intellectual Ventures	<ul style="list-style-type: none"> <li>• 25-30k U.S. Patent Publications</li> <li>• Many subsidiaries</li> <li>• Known as the “mother of all patent trolls”</li> <li>• Formed in 2000 by two former Microsoft employees</li> <li>• Nathan Myhrvold is the founder and has acquired more than 20,000 patents from universities, bankrupt corporations and independent inventors. The patents cover a wide variety of technologies ranging from lasers to computer chips.</li> <li>• Nathan owns roughly 10,000 to 12,000 patent families. His tactic is not to sue large corporations for infringement but instead to intimidate them with his distinction of being the largest patent holder in the U.S.</li> <li>• Intellectual Ventures says it has acquired 70,000 patents and patent applications</li> <li>• Combines legitimate research enterprises with patent licensing/enforcement units, where the latter form the basis of the companies' revenue stream</li> <li>• LED industry sectors: Power Management and Packaging</li> <li>• Most expensive patent licensing deals (between \$200 million and \$400 million per individual corporation)</li> <li>• No infringement claims, but instead uses stature to force businesses like Verizon, Cisco, Sony, Nokia, and Microsoft: into paying royalties so they won't be sued</li> <li>• Patent licensing firm, asserting a total of 181 patents in the cases it filed</li> <li>• Active in terms of portfolio as opposed to caseload</li> </ul>
Interdigital	<ul style="list-style-type: none"> <li>• 3571 U.S. Patent Publications; 1537 Patent Families; 39 Litigations</li> <li>• Interdigital develops wireless technology and also has a “comprehensive program” to protect its intellectual property</li> <li>• A licensing/enforcement organization that also performs research</li> <li>• LED industry sectors: Packaging</li> <li>• Derive majority of revenue from licensing IP to semiconductor manufacturers</li> <li>• Exploiting patent portfolios through licensing and litigation</li> </ul>
Lodsys	<ul style="list-style-type: none"> <li>• Targets app developers for using technologies to perform in-app upgrades -a feature that companies like Apple and Google provide to those developers</li> </ul>

<p>MPHJ Technology</p>	<ul style="list-style-type: none"> <li>• Scanner tro11; claims to own the technology covering scan-to email and demands that companies pay up nearly \$1000 or \$1200 per employee for using it or sign a document swearing not to use.</li> <li>• Innovative patent tro11 that sued the U.S. Federal Trade Commission</li> <li>• First patent tro11 targeted by FTC, and has been sued by the states of VT and NY</li> <li>• MPHJ began sending letters in September 2012. It did not file an infringement suit until November 18, 2013-after it had been sued by the states of Nebraska and Vermont.</li> <li>• Owned by Jay Mac Rust</li> <li>• Acquired its patents for a single do11ar</li> <li>• Instead of suing large tech outfits, it goes after sma11 businesses</li> <li>• Targets the customers who purchased the products and not the tech giants that make scanners and photocopiers</li> <li>• 101 subsidiaries, targeted over 16465 small businesses (sent letters nationwide)</li> <li>• More than 9000 letters claiming “most businesses, upon being informed that they are infringing someone’s patent rights, are interested in operating lawfu11y and taking a license promptly” and that “many companies have responded to this licensing program in such a manner.” The letters also claimed that the price for a license was reached through the responses of “many companies.” However, when the first 7,366 of those letters were sent, MPHJ hadn’t sold as ingle license though its “licensing program.”</li> <li>• Of the 16,465 letters that MPHJ sent, it only received 17 licenses.</li> <li>• MPHJ is using the letters to pressure the scanner manufacturers to pay them to not approach their consumers</li> </ul>
<p>Personal Audio</p>	<ul style="list-style-type: none"> <li>• Demands licenses from podcasters for podcasting despite the fact that most podcasters use off-the-shelf technology to distribute their podcast</li> </ul>
<p>Rambus</p>	<ul style="list-style-type: none"> <li>• 1555 U.S. Patent Publications; 674 Patent Families; 11 Litigations</li> <li>• Considered “the patent troll”</li> <li>• Made litigation its top money-making priority for more than a decade</li> <li>• Sanctioned for destroying evidence in its patent fight against SK Hynix Inc.</li> <li>• \$4 billion lawsuit against Hynix and Micron tossed out of court and wiped out 2/3 of company’s value</li> <li>• Stresses that it creates the technology it patents, and that the majority of its workers are engineers and inventors</li> <li>• A licensing/enforcement organization that also performs research</li> <li>• Partnered with GE and LED lighting; LED industry sectors: Fixtures, Components, Power Management, LED control, and Epitaxy</li> <li>• Derives majority of revenue from licensing IP to semiconductor manufacturers</li> <li>• Mixture of investing in R&amp;D and delivering technologies and exploiting patent portfolios through licensing and litigation</li> <li>• Has sued HP, Broadcom, MediaTek, and STMicroelectronics</li> <li>• USPTO invalidated one of the patents Rambus used to intimidate Nvidia into settling on the basis of prior art</li> </ul>
<p>Rockstar Consortium LLC</p>	<ul style="list-style-type: none"> <li>• 2362 U.S. Patent Publications; 1868 Patent Families</li> <li>• Funded by tech giants including Apple and Microsoft to scrutinize successful products to see if they infringe thousands of patents</li> </ul>
<p>Tessera (TSRA)</p>	<ul style="list-style-type: none"> <li>• 1301 U.S. Patent Publications; 635 Patent Families; 20 Litigations Technologies Inc.</li> <li>• Began as a semiconductor maker but then realized its “core value” was in licensing its technology</li> <li>• They don’t have much in the way of a sales force, but they are expert intimidators and litigators</li> <li>• Combines legitimate research enterprises with patent licensing/enforcement units, where the latter form the basis of the companies’ revenue stream (licensing specifically to semiconductor manufacturers)</li> <li>• Licenses their portfolio of semiconductor packaging and imaging technology patents</li> <li>• LED industry sectors: Components, Power Management, Epitaxy, Packaging and Bonding</li> <li>• Mixture of investing in R&amp;D and delivering technologies and exploiting patent portfolios through licensing and litigation</li> <li>• Continued revenue growth requires them to acquire and author new patents to replace portfolio patents that expire or are determined to be invalid by the courts or government patent offices</li> </ul>

TQP Development	<ul style="list-style-type: none"> <li>• Newegg is the only company to challenge this troll and was asked to pay \$2.3 million. (experts testified in this suit about prior art, but Newegg still lost, so Newegg appealed)</li> <li>• Owned by Erich Spangenberg, the man behind IPNav, a firm that has sued over 1638 companies for patent infringement</li> <li>• Sued Apple, Google, Intel, and Samsung over the same encryption patent which was filed in 1989 by Michael Jones</li> <li>• All settled out of court and made \$40 million for TQP</li> </ul>
Wisconsin Alumni Research Foundation WARF	<ul style="list-style-type: none"> <li>• 2368 U.S. Patent Publications; 1714 Patent Families; 28 Litigations</li> <li>• Patents technologies invented by University of Wisconsin researchers and licenses those patents throughout the world</li> <li>• Gives \$45 million each year to fund more research</li> <li>• Recently listed it among NPEs that “reap the benefit of successful products without investing heavily in development, marketing, and logistics.”</li> <li>• A leader among universities in making money from its large patent portfolio</li> <li>• Earned the 10th-most patent licensing revenue last year (\$57.7 million) out of more than 140 universities surveyed</li> <li>• WARF itself knows it is considered an NPE</li> <li>• LED industry sectors: LED control, Epitaxy, and Packaging</li> <li>• Tried to patent human embryonic stem cells and couldn’t, but has two seminal stem cell patents. W ARF might appeal first decision</li> </ul>

1. All information taken from publicly available sources and not verified. Taken from: Assessing the Best Strategy When Confronted by a Patent Troll, Michael Lafeber and Karen McDaniels, the 2014 Midwest Intellectual Property Institute – September 18, 19, 2014.

## 2015 BioInterface Workshop & Symposium Event Highlights:

- **Excellence in Surface Science Award Presentation by:**  
Gail Naughton; Histogen Aesthetics, LLC
- **Keynote Presentation by:**  
Stu Williams; Cardiovascular Innovation Institute - University of Louisville
- Full Day Workshop on “Hemocompatibility Technologies, Models, and Testing”
- 7 Technical Sessions
- Student Town Hall Meeting & Poster Contest
- Multiple Networking Specific Receptions

...and more!!

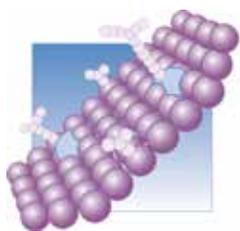
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- Help shape workshops and symposia that further the world-wide education of surface science
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- Your logo and a link to your website in the member directory on the official website of the Foundation, [www.surfaces.org](http://www.surfaces.org).
- Complimentary full page ad in SurFACTS, the Foundation's newsletter and discounts on all advertising.

# Thank You to Our Members!

