SurFACTS in Biomaterials

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Welcome From President Rob Kellar

Hello Colleagues of the Surfaces in Biomaterials Foundation,

I imagine everyone is in the hustle and bustle of the holiday season. I wanted to take a moment of your time and reflect back on our 2018 year in the Foundation and foreshadow to the upcoming 2019 year. First, I'd like to thank Chris Jenny, past president of the Foundation, for his leadership in 2018 and for an extremely successful Biointerface Conference in Boulder, CO. Boulder represented a second year of a new venue location for the Foundation and attracted premier session talks, industrial sponsors, and attendees. In 2019, we are going to continue with the new venue theme as we plan to visit the Salt Lake City, Utah, area for our Annual Biointerface Conference. We have already begun the planning for the Biointerface 2019 Workshop and Symposium; please continue to visit our **website** for upcoming details such as hotel venue location and abstract submission deadlines.

Our professional Foundation depends on strong investments and support from our members and sponsors. To those of you who are members and sponsors, thank you. I ask you to renew your commitments to our Foundation for 2019 and to help us recruit new professionals to join our efforts. For nonmembers, I urge you to formalize your membership and involvement in the Foundation. We have many places of need in 2019. These areas of service include Program Committee, Membership Committee, and Foundation sponsorship. Please feel free to reach out to me directly if you are interested in getting more involved in our Foundation.

On behalf of the Surfaces in Biomaterials Foundation, I wish you and your families a wonderful holiday season and a Happy New Year. I'll see you in Park City, Utah, for our Biointerface 2019 Workshop and Symposium from Sept. 4–6, 2019 … mark your calendars!

Rob Kellar, SIBF President
rskellar@des-company.com

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

Anna Belu Named Surface Science Award Winner

The Excellence in Surface Science Award is the highest honor given by the Surfaces in Biomaterials Foundation and recognizes an individual that has advanced the field of biomedical surface science or the practical application of surface science in the biomedical industry. This year the award committee recognized Dr. Anna Belu from Medtronic for her numerous contributions and leadership. The Foundation thanks Anna for all her hard work and dedication to advance the field.

Anna Belu is a Senior Principal Scientist, Technical Fellow and Bakken Fellow at Medtronic plc in Corporate Science and Technology. Anna has over 25 years of experience in surface science, materials, and characterization, with a keen focus on medical devices and the biointerface for the past 20 years. At Medtronic, Anna leads the Microscopy and Surface Analysis team, is Chair of the Analytical Lab Council, and is Liaison to Coronary Structural Heart R&D. Anna received her B.S. in Chemistry from Denison University in Ohio, her Ph.D. in Analytical Chemistry from the University of North Carolina, and spent two years as a postdoctoral fellow at the University of Washington in the Department of Bioengineering. Her first industrial position was with Physical Electronics as a Staff Scientist for four years.

Anna's enthusiasm for knowledge sharing and collaboration is evident through organizing symposia and conferences, and giving many invited talks and tutorials in the fields of surface analysis and biomaterials. Anna has over 40 publications. She has held leadership positions with several technical organizations, including Medtronic's Technical Forum, the Society for Biomaterials, the Surfaces in Biomaterials Foundation, and the American Vacuum Society (AVS). Anna is a Fellow of the AVS and is currently serving as Trustee. She is a member of the Scientific Committee for the International Conference on Secondary Ion Mass Spectrometry (SIMS) and is Chair of the conference in 2021. Anna is an Associate Editor of the journals Biointerphases and Surface Science Spectra, and previously served as Editor of Biointerphases for four years.

Past Award Recipients

- Victoria E. Carr-Brendel — 2017
- Antonios G. Mikos — 2016
- Gail Naughton — 2015
- Thomas J. Fogarty — 2014
- David Grainger — 2013
- Marcus Textor — 2012
- Nicholas A. Peppas — 2011
- David F. WIlliams — 2010
- Gabor Somorjai — 2009
- Ken Stokes — 2008
- Al Mann — 2007
- Robert Ward — 2006
- Jack Bokros — 2005
- Julio Palmaz — 2004
- David Castner — 2003
- J. William Costerton — 2002
- Stuart K. Williams — 2001
- James Anderson — 2000
- George Whitesides — 1999
- Richard VanDuyne — 1996
- Joseph Andrade — 1995
- Buddy Ratner — 1991

In Vivo Comparison of Porous Polymer-Coated and Bare Metal Coils for Aneurysm Occlusion

Herting, S.[1] Ding, Y.H.,[2] Boyle, A.J.,[1,3] Dai, D.,[2] Nash, L.D.,[1,3] Jessen, S.,[1] Mullen, A.,[1] Asnafi, S.,[2] Jakaitis, D.R.,[2] Johnson, C.R.,[2] Yeh, C.,[3] Friedemann, M.,[1] Clubb, F.J.,[1] Kallmes, D.F.,[2] Kadirvel, R.,[2] and Maitland, D. J.[1,3]

An intracranial aneurysm (ICA) is an abnormal ballooning of a blood vessel in the brain caused by an excessively stressed or weakened blood vessel wall. If ruptured, ICAs lead to subarachnoid hemorrhage, which is fatal in 25-50% of cases and leaves up to 30% of survivors permanently disabled. Bare platinum coils (BPCs) have been used extensively for occlusion of intracranial aneurysms since the first versions, Guglielmi Detachable Coils, were cleared for clinical use by the FDA in 1995. This treatment has been beneficial for many patients, but is also susceptible to recanalization at rates of 17-34%. Recanalization occurs when blood creates a new path to flow into the aneurysm. This can happen if compaction of the coils is induced by the hemodynamic stress of the blood flow or if part of the neck of the aneurysm was not completely filled with devices, and recanalization can require additional treatment to prevent rupture.

Recently, our lab at Texas A&M developed a polyurethane shape memory polymer (SMP) foam, and we've compared it's efficacy in experimental aneurysms to traditional platinum coils. This SMP foam induced rapid thrombus formation, thicker neoendothelialization, and accelerated healing in the aneurysms. Despite superior healing, the clinical use of SMP foam in aneurysm embolization is limited by the deliverability and radiolucency of the material. To address these limitations, our lab developed a SMP foam-coated coil (FCC) device prototype that utilizes a platinum coil backbone to maintain similar radiopacity and deliverability to traditional devices, but enables the delivery of SMP foam to facilitate tissue healing. Clinician feedback on the deliverability has been positive, and our most recent study aimed to evaluate aneurysm healing *in vivo* after treatment with SMP FCC devices to enable future clinical adoption.

In this study, we utilized a rabbit elastase-induced aneurysm model that was developed at the Mayo Clinic in Rochester, MN, where these studies were completed. This model exploits the elastase enzyme to break down a blood vessel wall similar to what would be observed in human patients. SMP FCC devices or bare platinum coil devices were used to treat these aneurysms for 30, 90, or 180 days to observe the progression of the healing responses.

At all time points, the neoendothelial tissue was thicker in the SMP FCC group, which is beneficial because this tissue can serve as a barrier to recanalization or thrombus formation in the parent artery. Connective tissue scores and healing scores assigned by an experienced pathologist were also higher in the SMP FCC group after 180 days. The connective tissue deposition can support the coil mass to prevent compaction. These results indicate that the SMP FCC devices have potential to improve endovascular treatment of aneurysms by providing a scaffold for tissue healing. Another interesting finding of this study was that the degradation rate of the SMP foam was faster in this rabbit aneurysm model than had been observed previously in a pig model. This is likely due to a difference in the inflammatory response of a rabbit compared to a pig because the foam degrades in response to oxidative species generated during this process. In the future, we will investigate these different inflammatory responses and how they may influence healing in addition to continuing the development of the SMP FCC device with the goal of clinical translation.

1. Texas A&M University, College Station, TX
2. Mayo Clinic, Rochester, MN
3. Shape Memory Medical, Santa Clara, CA

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Multifunctional Material for the Detection and Killing of Bacteria for Use in Medical Devices

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According to the CDC, total costs due to hospital-acquired infections total over $35 billion in the United States alone, many of which are due to device-related infections.[1] This epidemic creates a critical need for researchers to develop better methods for the detection and treatment of bacterial infections. A multifunctional material that could perform both functions would offer improved efficiency and versatility while reducing costs.

Accurately detecting when a patient has a bacterial infection is critical to preventing the over-use of antibiotics.[2] In this work, a bacterial enzyme-activated biosensor is synthesized. The amino acid proline is attached to a fluorescent aminoacridone compound, and is cleaved by prolyl aminopeptidase, a bacterial enzyme that cleaves N-terminal proline from peptides, causing a color change of the compound.[3] This enzyme is found in Pseudomonas aeruginosa, a bacteria species that is growing increasingly resistant to antibiotics and causes a significant amount of hospital-acquired infections.[4]

In addition to detecting bacterial infections, new antibacterial materials are in critical demand. Nitric oxide (NO) is an excellent small molecule candidate for use as an antibacterial agent, as it has broad spectrum antibacterial activity and it is difficult for bacteria to develop resistance to it.[5–7] NO is typically delivered as a prodrug NO donor, which is metabolized into free radical NO due to a change in environment.

In this work, a dual-function compound is synthesized to both detect and kill bacteria, process shown in Figure 1. An NO donor is attached to the fluorescent biosensor to add antibacterial activity. The compound spontaneously releases NO via the NO donor in solution, then the bacterial enzyme cleaves proline, changing the fluorescent color of the compound from blue to yellow.

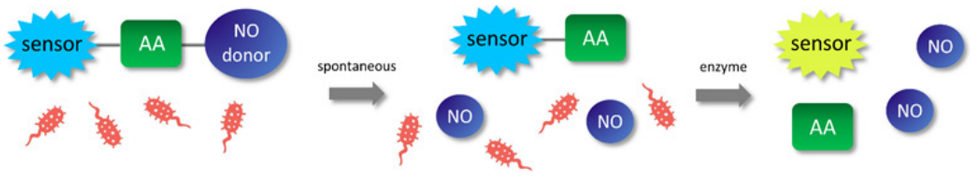

Fig. 1: Schematic showing nitric oxide release and color change of biosensor. Nitric oxide is released from the nitric oxide donor group spontaneously, killing Pseudomonas aeruginosa bacteria cells. A bacterial enzyme then cleaves proline from the fluorescent aminoacridone/proline compound, changing the color from blue to yellow.

Beginning with an inexpensive starting material, a biosensor that changes its fluorescent color when attached to the amino acid proline is synthesized via a five-step procedure. Bacterial studies performed with P. aeruginosa show that the compound changes color in the presence of bacteria. When P. aeruginosa is present, the prolyl aminopeptidase enzyme it produces cleaves proline from the biosensor, producing a clear color change from blue to yellow under UV light (Figure 2), providing a visual cue when bacteria are present.

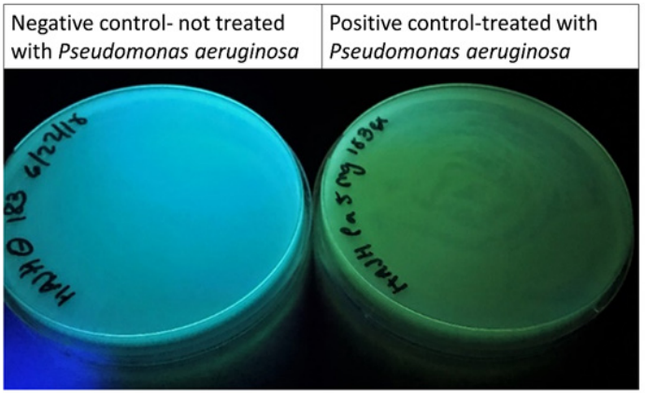

Fig. 2: Representative agar plates showing color change of biosensor from blue to yellow under a 365 nm UV lamp in the presence of Pseudomonas aeruginosa, as expected. Left: negative control- not inoculated with Pseudomonas aeruginosa, appears blue; right- inoculated with Pseudomonas aeruginosa, appears yellow.

With the detection component demonstrated, an NO donor is attached to the biosensor in one step to add antibacterial activity. The overall six step procedure requires significantly fewer steps than typical antibiotic syntheses and gives a much higher yield. The amount of NO released from the compound is measured to be in a therapeutically relevant range. P. aeruginosa is exposed to the fluorescent NO donor compound, and a cell viability assay is performed to determine the antibacterial activity of the compound. The assay shows that the compound is able to kill bac-

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Rapidly Curing Chitosan Calcium Phosphate Composites as Dental Pulp Capping Agents

Matthew J. Osmond and Melissa D. Krebs
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Dental caries affect over 90% of the population worldwide. Left untreated, these infections can result in tooth loss, gum disease, and in extreme cases sepsis-related fatalities. Early stage caries with erosion of enamel and dentin hard tissues are treated by removal of the infected region followed by restoration of tooth function with placement of permanent metal amalgams or composite fillings. For the duration of the patient's lifetime, the fillings require consistent maintenance and are at high risk for the formation of secondary caries which would require additional corrective procedures. With increased severity of a cavity, there is an increased risk of infection of the dental pulp, which often results in the need for a root canal. Thus, there is a need to develop a pulp capping material that improves on the current technology using rational design.

These regenerative capping agents were designed to improve the current agents that are currently available on the market. The aim is to create a product that is injectable, rapidly curing, and both biologically and mechanically suitable to grow and differentiate dental cells while providing protection for the underlying dental pulp.

To achieve this, a composite material comprised of functionalized chitosan crosslinked with a fast reacting diglycidyl ether and laden with calcium phosphate nanoparticles was used. Carboxymethyl-chitosan (CMCS) was used because it improves the solubility and reaction speed of the polymer matrix, and it is derived from widely available chitosan feedstock. 1,4 butanediol diglycidyl ether was used because it is water soluble and will react rapidly with deprotonated primary amines found on the CMCS. These newly engineered materials currently will cure in 10-20 minutes or less.

Calcium phosphate particles are used as the composite filler as they have been shown to have excellent mechanical strength and a high potential to differentiate stem cells into the bone or dental cells that are found in mineralized tissues. Four types of calcium phosphate are used to determine the best mineral morphology for mechanical strength and odontogenic capacity. Differences in synthesis and maturation methods result in a variety of different mineral morphologies, shapes, and sizes. All particles were synthesized using solution precipitation of calcium nitrate and ammonium phosphate to form dicalcium phosphate dihydrate (DCPD). Tetraethylene glycol dimethacrylate (TEG) functionalization of the surface was used to prevent agglomeration, with the hypothesis that this would aid in increasing the mechanical strength of the composite. These DCPD particles were then matured in solution to form hydroxyapatite HA particles [1]–[3]. HA is the native mineral found in bones and dentin and has increased odontogenic potential over DCPD.

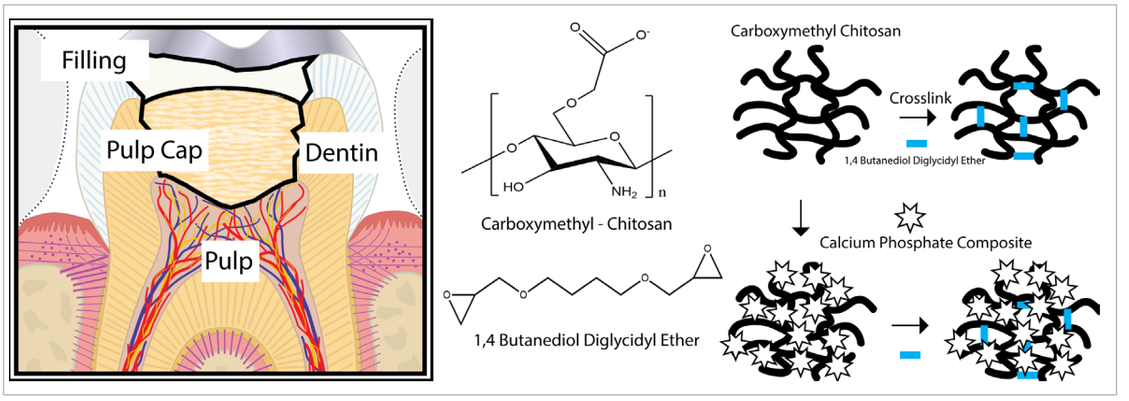

Fig. 1. (Left) Anatomy of a tooth, displaying the location of the dental pulp, the pulp cap and the surrounding dentin and enamel layers. (Center) Illustration of the constituents that make up the dental fillings. (Right) Schematic that shows how the composites are made.

Transmission electron microscopy (TEM) images of the particles show varied morphologies: the DCPD particles are small (~20 nm) and the addition of TEG decreases the agglomeration of the particles. After

Rapidly Curing Chitosan ... continues on pg. 6

BioInterface 2018 Attendees in Boulder, Colorado

Thank you to all who participated in the BioInterface 2018 Workshop and Symposium in Boulder, Colorado. We would like to recognize our Gold Sponsors, Abbott, DSM Biomedical Inc., Medtronic and W.L. Gore & Associates, Inc.for your contributions to making BioInterface 2018 a success. The Workshop titled “3D printing in medical devices”, co-chaired by Angela DiCiccio and Dan Gostovic, kicked off the 3 day event. The Keynote Lecture by Jeff Karp addressed “Tools for accelerated medical innovation” on Monday afternoon after the Workshop. The Symposium on Tuesday and Wednesday was filled with informative sessions. Thank you to Qualia Medical as a session sponsor of Neurological Devices and Axolotl Biologix as a session sponsor of Tissue Engineering / Regenerative Therapies. BioInterface 2018 included an additional bonus of hosting the student poster sessions at BioFrontiers Institute at the University of Colorado Boulder with Larry Gold speaking at the end about “The confluence of engineering and health monitoring”. Congratulations to our student poster winner Hailey Hibbard from the Colorado State University. Stay tuned to learn more about the BioInterface 2019 Workshop and Symposium. Follow us on Facebook, Twitter and Linked in for the most updated information.

Rapidly Curing Chitosan Calcium Phosphate Composites as Dental Pulp Capping Agents ... *continued from pg. 5*

the conversion of the particles to HA, the particles bind to form larger (~500 nm) platelet-like structures.

These materials were fabricated and tested for mechanical properties and biocompatibility. The compressive modulus was measured to be greater than 1 MPa for all particle types and was significantly higher for composites made with HA particles compared to DCPD particles. Biocompatibility was examined by seeding dental pulp stem cells on the surface in vitro and measuring the relative DNA content over four weeks. Materials containing HA had greater proliferation than those containing DCPD.

Our future work includes the further improvement of the mechanical properties of these composite materials, and improvement of cell migration and cell differentiation in response to the materials. Here, we demonstrate a new class of biomaterial composites as injectable, rapidly curing, bioactive pulp capping agents.

1. ***J. L. Harding and M. D. Krebs, “Controlled and Tunable Biomimetic Apatite Mineralization of Synthetic Hydrogels,” Macromol. Mater. Eng., 2016.***

2. ***J. L. Harding and M. D. Krebs, “Bioinspired Deposition-Conversion Synthesis of Tunable Calcium Phosphate Coatings on Polymeric Hydrogels,” ACS Biomaterials Science & Engineering, vol. 3, no. 9, pp. 2024–2032, Sep. 2017.***

3. ***J. L. Harding, M. J. Osmond, and M. D. Krebs, “Engineering Osteoinductive Biomaterials by Bioinspired Synthesis of Apatite Coatings on Collagen Hydrogels with Varied Pore Microarchitectures,” Tissue Engineering Part A, vol. 23, no. 23–24, pp. 1452–1465, Dec. 2017.***

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continued from pg. 4

teria, causing a 55-75% reduction in the number of bacteria at a 10 mM dose. A color change is also apparent after NO was released, demonstrating the dual-function of the compound.

These experiments provide proof-of-concept of the first dual-function small molecule to detect and kill bacteria. In the future, the sensing therapeutic could be used in a medical device coating to indicate when an infection has set in, as well as treating the infection. Color-changing materials could also be made, such as antibacterial bandages, gels, or sprays.

The details of this work have been submitted for consideration for publication to the Journal of Materials Chemistry B on Sept. 27, 2018.

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2. *Ventola, C. L. The Antibiotic Resistance Crisis: Part 1: Causes and Threats. P T Peer-Rev. J. Formul. Manag. 2015, 40 (4), 277–283.*
3. *Peng, C.-T.; Liu, L.; Li, C.-C.; He, L.-H.; Li, T.; Shen, Y.-L.; Gao, C.; Wang, N.-Y.; Xia, Y.; Zhu, Y.-B.; et al. Structure–Function Relationship of Aminopeptidase P from Pseudomonas Aeruginosa. Front. Microbiol. 2017, 8, 2385.*
4. *Schaberg, D. R.; Culver, D. H.; Gaynes, R. P. Major Trends in the Microbial Etiology of Nosocomial Infection. Am. J. Med. 1991, 91 (3), S72–S75.*
5. *Moncada, S.; Higgs, E. A. The Discovery of Nitric Oxide and Its Role in Vascular Biology. Br. J. Pharmacol. 2006, 147 (S1), S193-201.*
6. *Nathan, C. F.; Hibbs, J. B. Role of Nitric Oxide Synthesis in Macrophage Antimicrobial Activity. Curr. Opin. Immunol. 1991, 3 (1), 65–70.*
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