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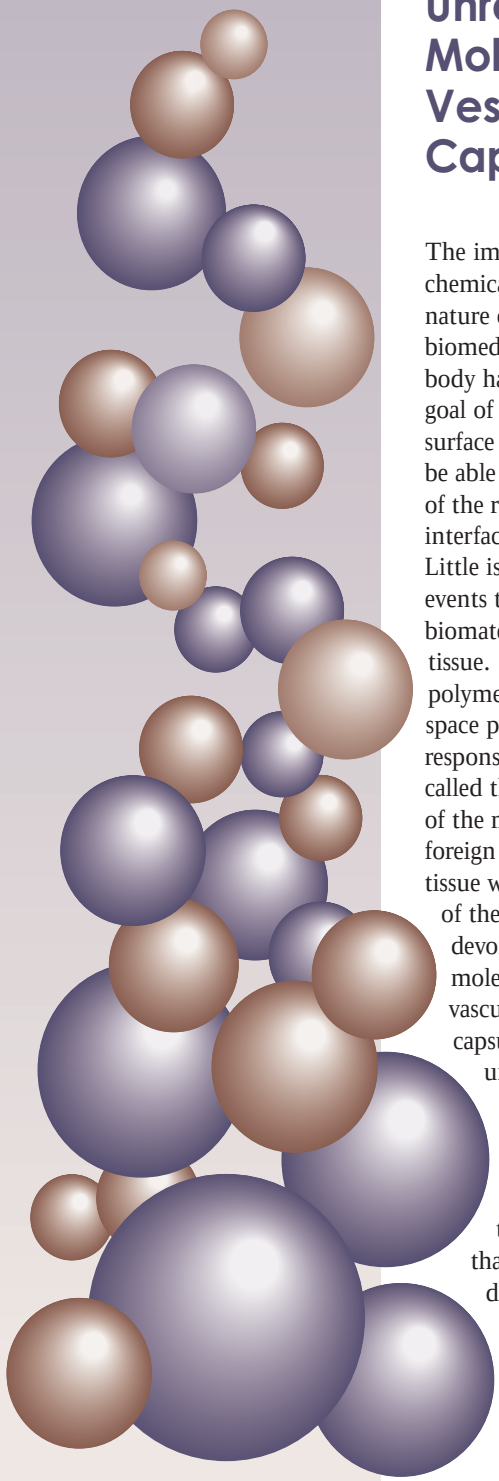
13355 Tenth Avenue North ● Suite 108 ● Minneapolis, MN 55441-5510 ● (763) 512-9103 phone ● (763) 765-2329 fax ● www.surfaces.org



Unraveling Mysteries at the Biointerface: Molecular Mediator of Inhibition of Blood Vessel Formation in the Foreign Body Capsule Revealed

By James Brauker, DexCom, Inc.

The importance of understanding the chemical, physical, and geometrical nature of the materials used in biomedical devices implanted in the body has long been recognized. The goal of understanding the nature of the surface of biomaterials is, of course, to be able to direct and control the nature of the reactions of the tissues at the interface with the biomaterial surface. Little is known about the molecular events that occur at the biointerface of biomaterials implanted in connective tissue. A wide variety of non-toxic polymers implanted in the subcutaneous space produce eerily similar tissue responses in the form of fibrotic tissue called the foreign body response[1]. One of the most striking features of the foreign body response is that the fibrotic tissue within 50-100 µm of the surface of the biomaterial interface is usually devoid of blood vessels. The molecular mechanisms preventing vascularization of the foreign body capsule have been little understood until recently.

To understand these molecules and mechanisms of the foreign body response, we must turn to the biologists and biochemists that have spent the last several decades identifying the cellular and molecular reactions in the extracellular matrix. At the University of Washington in Seattle, a merger of biomaterials scientists and extracellular matrix biochemists occurred several years ago in the National Science Foundation (NSF)-supported ERC (Engineering Research Center) known as the UWEB (University of Washington Engineered Biomaterials), an academic member of the Surfaces in *Biomaterials* Foundation. Biomaterials research money and collaborations became available to fund laboratories that had long been doing basic biochemical research. Because of this cross-disciplinary effort, the role of matricellular proteins like secreted protein, acidic and rich in cysteine (SPARC), thrombospondin, and osteopontin began to be studied in the applied science of biomaterials. Because of this, an astounding breakthrough in the understanding of the mechanisms of how blood vessels may be inhibited in the foreign body response occurred.

In Paul Bornstein's lab, Themis Kyriakides was interested in the role of the matricellular protein called thrombospondin 2 (TSP2) in development of the mouse. To do so, he built a new mouse using the tools of modern biochemistry[2]. The mouse (a transgenic "knockout" mouse) lacked expression of the gene for thrombospondin 2. Therefore, any abnormalities in the mouse as it developed must be in some way related to the expression of TSP2. The mice grew to adulthood, and appeared

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Executive Editor
Joseph A. Chinn
Sulzer Carbomedics, Inc.
1300 East Anderson Lane
Austin, TX 78752-1793
512-435-3347 phone
512-435-3317 fax
jchinn@carbomedics.com

Managing Editor
Paul M. Stone
Surfaces in *Biomaterials* Foundation
13355 Tenth Avenue North, Suite 108
Minneapolis, MN 55441-5554
763-765-2310 phone
763-765-2329 fax
pstone@surfaces.org

Biology Editor
Daniel Mooradian
Bio-Vascular, Inc.
2575 University Avenue
St. Paul, MN 55114-1024
651-603-3746 phone
651-642-9018 fax
d.mooradian@biovascular.com

Characterization & Analysis Editor
James Marotta
Advanced Product Technologies
Smith & Nephew
1450 Brooks Road
Memphis, TN 38116
901-399-5145 phone
901-399-6020 fax
james.marotta@smith-nephew.com

Modification Editor
Byron Shen
SurModics, Inc.
9924 West 74th Street
Eden Prairie, MN 55344-3523
952-829-3285 phone
bshen@surmodics.com

Regulatory Editor
Elaine Duncan
Paladin Medical, Inc.
P.O. Box 560
Stillwater, MN 55082
715-549-6035 phone
715-549-5380 fax
duncan@paladinmedical.com

Advertising Manager
the ARDEL group
13355 Tenth Avenue North, Suite 108
Minneapolis, MN 55441-5554
763-512-9103 phone
763-765-2329 fax
visibility@surfaces.org

From the President

by Lise W. Duran

This year, at the close of another successful Symposium and Workshop, Foundation members were given the opportunity to reflect upon who we are as an organization, why we began, and where we want to go. While recognizing that we must preserve our initial charter, we must also provide for technological changes and advancements that occur in our ever-evolving environment. Consequently, as we continue to move through this decade, many new and exciting changes will be taking place within the Foundation.

One of the main strengths of the Foundation has been to provide a multidisciplinary forum for industry, academia, clinicians, and regulatory bodies to discuss all aspects of the interface between materials and tissues. To better highlight this key role, beginning in 2002, the annual Symposium will be renamed "BioInterface." In addition, the Foundation will place more emphasis on broadening its discipline base to other communities that share interests in biointerfacial issues, e.g., pharmaceutical, bioadhesives, medical diagnostics, personal care, medical packaging, clinical and animal testing services, to name a few. Our new mission statement underscores these changes:

The Foundation is dedicated to exploring creative solutions to technical challenges at the BioInterface by fostering education and multidisciplinary cooperation among industrial, academic, clinical, and regulatory communities.

The Foundation is currently investigating how our members-at-large can become more involved in setting public policy with ISO, FDA, AIMBE, or HSMAI. We are exploring alternative education programs. Videoconferences with the FDA have been successful and, hopefully, we can expand on this in the future.

Next year's meeting will incorporate some format changes to reflect the new look of the Foundation. The program will comprise fewer session topics. This will allow for more question and answer time within each session. To enhance this further, we will train session chairs, as well as implement a time monitoring system to ensure that sessions run on schedule. The dedicated session on Surface Characterization will be eliminated; however, each paper will be required to include a section on surface characterization/analysis. The abstract format will also change and will now be two-column, one-page abstract, similar to the Annual Meeting of the Society For Biomaterials abstracts. In addition, electronic abstract submission will be used for our members' convenience.

The 2002 program hopes to include an evening "rump" session whereby a point-counterpoint on a hot topic will be colorfully presented. Each year, the Symposium will include a session presented by clinicians. We hope to begin in 2002 with a session on drug-coated stents. Other prospective session topics for next year include hemocompatible coatings, cell-based drug and gene delivery, animal models, and tissue engineering.

Stay tuned for these exciting changes and more. See you in Arizona, September 4-6, 2002, for one last year, then it is on to a new venue in Savannah, GA, for the 2003 meeting.

Highlights of Surfaces in *Biomaterials* 2001

By Karen Kazmierczak, Meeting Manager, and Mark Moore, Foundation President-Elect

The Surfaces in *Biomaterials* Foundation held its eleventh annual symposium August 29-August 31, 2001, at the Fairmont Scottsdale Princess. This year's program included a one-day workshop and a two-day symposium and exhibition.

The workshop was entitled *Roadmap to Successful Development and Regulatory Approval of Medical Devices with Hemocompatible Coatings* and was held on Wednesday, August 29. The program was transmitted directly to the FDA/Center for Devices and Radiological Health. This video conference allowed the FDA to participate in a panel discussion involving the process of bringing products with hemocompatible coating from manufacturing to market.

The symposium was held on Thursday, August 30 and Friday, August 31, 2001. The scientific sessions included cardiovascular, device-centered infection, gene and drug delivery, microfluidics and biosensors, opthalmic biomaterials and cell-surface interactions, sterilization of biomaterials, and surface analysis techniques.

The Cardiovascular session chaired by Dale Hauenstein included talks with a common theme of proper healing and performance of implantable cardiovascular materials. Among the talks were those addressing in-stent restenosis, drug release, growth factor modification of implantable materials, and approaches to mitigate bioprosthetic heart valve calcification. This session was rated by attendees as most relevant to their work.

The Awards Session recognized Dr. Stuart Williams, University of Arizona, for significant contribution to the field of surface science as the recipient of the 2001 Excellence in Surface Science Award. Also presented during this session was the David J. Lee Student Award recognizing excellence in student research. This year's recipient was Kameha R. Kidd, also from the University of Arizona. In addition, two new awards were presented. Paul L. Valint, Jr. was awarded Emeritus Membership in the Foundation for his work as a retired supporting member from Bausch & Lomb. Abbott Advance Drug Delivery received the first platinum donor award for its financial contributions to the symposium.

Stuart Williams, 2001 Excellence in Surface Science Award Winner

Supporting Members

Abbott Laboratories - Advanced Drug Delivery

Advanced Surface Technology, Inc.

Atrium Medical Corporation

Bausch & Lomb

Biocoat, Inc.

BioSet - Biosurface Engineering Technologies, Inc.

Carmeda AB

CIBA Vision Corporation

CR Bard

DexCom

Digital Instruments, Inc.

Evans Analytical

W. L. Gore & Associates, Inc.

Medtronic Promeon Division

Physical Electronics, Inc.

STS Biopolymers, Inc.

Sulzer Carbomedics, Inc.

Surface Solutions Labs Inc.

SurModics, Inc.

Union Carbide Corporation

United Chemical Technologies, Inc.

Academic Members

Arizona State University

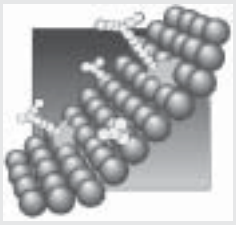
Massachusetts Institute of Technology

University of Arizona

University of Minnesota

University of Texas, CEBBI

University of Washington - NESAC/BIO



Mysteries

(continued from page 1)

outwardly normal, but had many unusual characteristics related to extracellular matrix. Perhaps the most striking observation was that the mouse had much denser networks of blood vessels than normal mice. Kyriakides and Bornstein were suddenly engaged in something that drew the interest of Buddy Ratner, Director of the UWEB. Ratner and colleagues provided funding, as well as methods and materials to determine if the foreign body response around implanted materials would be altered in the mice lacking TSP2[3]. Silicone rubber discs were implanted in the subcutaneous tissue of adult mice. After 4wk in the tissues, the explanted discs from mice lacking the TSP2 gene mounted a foreign body response, except that it was highly vascularized. Normal mice mounted a typical avascular foreign body response. These results showed unequivocally that TSP2 plays a role in inhibition of vascularization in a foreign body response[3].

More recently, Kyriakides and colleagues published a follow-up paper in which they showed that normal mice could be induced to form an altered foreign body response by interrupting TSP2 synthesis in the cells responding to a biomaterial implant[4]. They implanted polyvinyl alcohol (PVA) sponges with a Gene-Activated Matrix (GAM) containing antisense cDNA that interferes with the expression of TSP2. Their hypothesis was that if the cells reacting to the implant were to take up and express the antisense, then the expression of TSP2 would be inhibited, which it was four weeks post-implant. Histology showed an altered foreign body response with increased blood vessel formation and collagen deposition. Controls implanted in the same animals formed classical avascular foreign body capsules. Conversely, when they implanted GAM containing sense cDNA for TSP2 into TSP2 knockout mice, cells in the region of the PVA sponge synthesized TSP2.

The latter study not only provides further evidence for the role of TSP2 in controlling the foreign body response, but also may lead to a practical approach to improve the tissue reaction at the biointerface in the future. Like the UWEB, the Surfaces in *Biomaterials* Foundation is primarily focused on the interface between biomaterial implants and tissues. We are poised at the beginning of a new era in biomaterials research that will result in an eventual understanding of how to exploit and control the extracellular matrix using the mind-bending tools of modern molecular biology. The Surfaces in *Biomaterials* Foundation is uniquely qualified to serve as a venue for the advancement of molecular studies of the interface between materials and tissues.

References

1. Brauker, JH *et al.* Neovascularization of Synthetic Membranes Directed by Membrane Microarchitecture. J. Biomed. Mat. Res. 1995 29: 1517-1524.

2. Kyriakides TR, *et al*. Mice that lack thrombospondin 2 display connective tissue abnormalities that are associated with disordered collagen fibrillogenesis, an increased vascular density, and a bleeding diathesis. J. Cell Biol. 1998 Jan 26; 140(2): 419-430.

3. Kyriakides TR, *et al*. Mice that lack the angiogenesis inhibitor, thrombospondin 2, mount an altered foreign body reaction characterized by increased vascularity. Proc. Natl. Acad. Sci. U.S.A. 1999 Apr 13; 96(8): 4449-4454.

4. Kyriakides TR, *et al*. Regulation of angiogenesis and matrix remodeling by localized, matrix-mediated antisense gene delivery. Mol. Ther. 2001 Jun; 3(6): 842-849.

FDA Educational Lecture Series

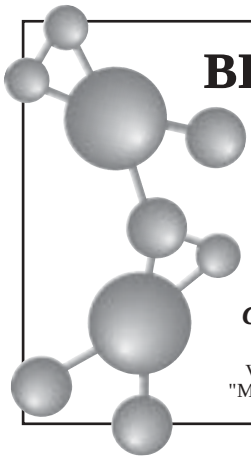
By Lise W. Duran, President

The Foundation is facilitating the development of a course curriculum on Surfaces in Biomaterials for the FDA that will be offered this winter. This course will focus on methods of coating and surface modification being developed and used by medical device manufacturers, current applications, and techniques used for analysis. For each type of method this course will address:

- what is added or changed, physically or chemically
- how the coating/modification is done
- how the coating/modification is characterized or measured
- what is the effect at the tissue interface
- what are the clinical effects and applications
- what are the regulatory issues

The target audiences for this course are reviewers from the Offices of Device Evaluation (ODE), Science and Technology (OST), and Surveillance and Biometrics (OSB) within the Center for Devices and Radiological Health (CDRH). These reviewers are responsible for analyzing, recommending, and/or taking regulatory action on medical device submissions that utilize these technologies.

This course will be presented in lecture format with speakers from CDRH, academia, and industry blended with examples to illustrate and reinforce applications and concepts presented. The course will begin in January and will run approximately 12 weeks. Industry participants are invited to present a 3-4 hour lecture on their biomaterial coating or surface modification technology. The course will be held in Rockville, MD at CDRH. Participants will be responsible for all of their own travel arrangements and expenses. Those interested in presenting a lecture, please contact Sandy Hofman at shofman@ardel.com. The participants will be selected on a first-come, first-served basis, so please respond as soon as possible!



BIOINTERFACE 2002

September 4-6, 2002
Fairmont Princess
Scottsdale, Arizona, U.S.A.
Call for Papers Deadline: May 10, 2002
Visit www.surfaces.org and click on "Meetings" for submission information.

Introducing New Electronic Abstract Submission Process

Surfaces in *Biomaterials* Foundation will join the electronic age in abstract submission for the 2002 Annual Symposium. This easy to use process should be a pleasure to all submitters.

The abstract submission system will be available for use beginning February 1, 2002. The process begins with submitters visiting the Surfaces in *Biomaterials* Foundation website www.surfaces.org and clicking on Meetings. Prompts will guide authors to create their own user names and passwords to enable entry into the actual submission site. Once an author has created a user name and password, the system will remember the author on each and every entry into the abstract submission system.

Take some time to review the abstract preparation page, sample abstract page, and online submission instruction page for detailed information regarding required abstract sections, suggested abstract sections, formatting, fonts and types. For ease of submission, prepare abstracts in Microsoft Word and convert to Rich Text Format (rtf) for a successful upload of your document. Please utilize the template on the abstracts page to ensure proper formatting. After a successful upload of abstracts, authors receive a confirmation number.

Editing is quite simple as well; revisit the submission site and follow the prompts to EDIT. Abstracts will be limited to a single page with two columns. All submissions and edits must be completed by May 10, 2002, the abstract submission deadline.

Because of the clear, helpful information included on the Surfaces in *Biomaterials* Foundation's website, submitting abstracts for the 2002 Annual Symposium in Scottsdale, Arizona, will be almost as easy as addressing an envelope and licking a stamp. If you do require some assistance or have any questions, the Surfaces in *Biomaterials* Foundation Educational Services team members are ready and willing to serve you. Just give them a call at (763) 765-2345.

This dynamic, easy abstract submission system ensures a great start to BioInterface 2002. See you in Scottsdale September 4-6, 2002!

2001-2002 Board Members Announced!

Congratulations are extended to the newly elected members to the 2001-2002 Surfaces in *Biomaterials* Foundation's Board of Directors. Jim Brauker of Dexcom, Inc. was elected as Vice President, and Peg Opolski of Surface Solutions Labs, Inc. fills the elected position of Secretary. Congratulations also to Larry Salvati who has been re-elected to his new role of Treasurer. Please join the Foundation in congratulating these members on their election to office!

Peter Tarcha, 2000-2001 President, presents the Presidential Plaque to Lise Duran, 2001-2002 President.

Custom Designed Feedthrus for Pacemaker and Defibrillator Manufacturers

Morgan Advanced Ceramics-New Bedford (MAC-New Bedford), formerly Alberox, a world leader in ceramic-to-metal assemblies and metal injection molding (MIM), offers custom-designed, hermetic power feedthrus for pacemaker and defibrillator manufacturers. Designed to provide superior reliability and durability, these components feature MAC-New Bedford's innovative ceramic to metal seal assembly technology. The custom designed components meet the specific needs of each customer for virtually the same price as other "standard" offerings.

MAC-New Bedford's ceramic-to-metal solutions for the medical device industry are constructed from biocompatible metal components and high purity Alumina ($A1_20_3$) ceramic. This ceramic-to-metal design allows for cost-competitive manufacturing through a consistent, repeatable process. The design flexibility enables components to be produced to the customer's specification at a lower total cost.

Offering thermal shock resistance and constructed of biocompatible, corrosion-resistant materials, the feedthrus are ideal for implants and can withstand extreme conditions. MAC-New Bedford can manufacture smaller feedthrus while maintaining superior strength and electrical properties because of the ceramic-to-metal process. All implant assemblies are 100% traceable for both process and component materials, and they are produced in an ISO9002 certified facility.

(Source: Press Release)

New Surgical Sealant Technology

BTG, the global technology commercialization company, will commercialize the rights to a new surgical sealant technology, which could replace traditional suturing in surgery, as well as provide advantages over biochemical sealants currently in use.

Originally designed for ophthalmic surgery – but also applicable in general surgery – the technology has many advantages over existing suturing techniques. The viscosity and material characteristics of the sealant allow greater flexibility of use during surgery. It also contains greater cohesive properties than fibrin adhesives, allowing a faster completion of the procedure and reduced healing time for incisions. This sealant has a lesser exothermic reaction than current cyanoacrylic adhesives and will not cause tissue ulceration, minimizing the risk of patient rejection. As the incision heals, the sealant is reabsorbed into the body and eliminated naturally. Fibrin adhesives are absorbed *in vivo*, but in contrast, are prone to viral contamination. As well, the sealant is transparent, which is ideal for ophthalmic surgery.

The technology consists of two products with complementary applications to suit the unique demands of different surgical procedures: 1) ADALÒ 1, an adhesive which provides strong adhesion and quick polymerization, and 2) ADALÒ 2, a sealant which offers slower polymerization, high flexibility and prolonged manipulation time.

(Source: Press Release)

Calendar of Events

Medical Design & Manufacturing (MD&M) West
February 4-7, 2002
Anaheim Convention Center
Anaheim, CA, U.S.A.
www.devicelink.com/expo/west02/

2002 AdvaMed Annual Meeting
March 3-6, 2002
Four Seasons Aviara Resort
Clarsbad, CA, U.S.A.
www.himanet.com/2002annualmeeting/index.html

University of Delaware, Engineering Outreach: The Next Frontiers
March 12-13, 2002
Trabant Center
University of Delaware
Newark, DE, U.S.A.
enggoutreach@udel.edu
www.udel.edu/engg/outreach/
302-831-4863/2401

American College of Cardiology ACC '02
March 17-20, 2002
Atlanta, GA, U.S.A.
www.acc.org/2002ann%5Fmeeting/home%5F02.htm

Australian Society for Biomaterials 2002 Annual Conference
March 19-21, 2002
Australian National University
Canberra, Australia
www.biomaterials.org.au

2002 MRS Spring Meeting
April 1-5, 2002
San Francisco, CA, U.S.A.
www.mrs.org/meetings/spring2002/cfp/

223rd ACS Ntional Meeting
April 7-11, 2002
Orlando, FL, U.S.A.
http://chemistry.org/

Medtrade Spring 2002
April 22-24, 2002
Sands Expo and Convention Center
Las Vegas, NV, U.S.A.
wwww.medtradewest.com/

Society For Biomaterials 28th Annual Meeting
April 24-27, 2002
Tampa Convention Center
Tampa, FL, U.S.A
registration@biomaterials.org
www.biomaterials.org
763-543-0908

82nd Annual Meeting of the American Association for Thoracic Surgery (AATS)
May 5-8, 2002
Washington, DC, U.S.A.
www.aats.org/doc/6270

ASM 102nd General Meeting
May 19-23, 2002
Salt Lake City, UT, U.S.A.
www.asm.org/mtgsrc/gm2002prelimprogtopppage.htm

Wound Healing Society 12th Annual Educational Symposium
May 28-June 1, 2002
Baltimore, MD, U.S.A.
www.woundheal.org

Associazione Italiana di Scienza Tecnologia delle Macromolecole (AIM) Europolymer Conference 2002
June 2-6, 2002
Gargnano, Italy
www.dcci.unipi.it/~bea/eupoc02

Medical Design & Manufacturing (MD&M) East
June 3-5, 2002
Jacob K. Javits Convention Center
New York, NY, U.S.A.
www.devicelink.com/expo/east01/

International Conference on Advances in Biomaterials for Reconstructive Medicine
June 9-14, 2002
Capri, Italy
www.area.na.cnri.it/itmc/

48th Annual ASAIO Conference
June 13-15, 2002
Hilton New York
New York, NY, U.S.A.
www.asaio.com

International Cartilage Repair Society: 4th ICRS Symposium
June 15-18, 2002
MTCC, Toronto, Canada
www.cartilage.org

Controlled Release Society 29th Annual Meeting
July 20-25, 2002
COEX World Trade Center and COEX Inter-continental Seoul
Seoul, Korea
www.controlledrelease.org

Surfaces in **Biomaterials** Foundation
13355 Tenth Avenue North, Suite 108
Minneapolis, MN 55441-5510