BioIntraface®: The Next Quantum in Medical Devices

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ABSTRACT

BioIntraface®, Inc., located in Riverside, Rhode Island, was formed in February of 2009 to commercialize its biomaterials surface treatment technologies. The platform technologies involve the creation of economical, multifunctional metal oxide and polymer materials and coatings to control the bioactivity and antimicrobial properties of medical devices and implants. Biointraface® has continued optimizing and validating coatings for promising applications in orthopaedics, dentistry, catheters, wound dressings, topical antimicrobial products, and cosmetics applications. It has also obtained third-party verification of ISO biocompatibility testing for eight coatings with increasing levels of antimicrobial agents, where no cytotoxicity was indicated and similar tests showing long lasting antimicrobial efficacy against multiple strains of bacteria.

KEYWORDS: antimicrobial coatings, medical devices, metal oxide and polymer coatings

UPGRADING THE SURFACE OF MEDICAL DEVICES

Silicones, such as polydimethylsiloxane (PDMS), have a long history of use in medical applications, beginning with a bile duct repair by Lahey in 1946,[1] an artificial urethra in 1948 by DeNicola[2] and a hydrocephalus shunt constructed by Holter for his son in 1956.[3] The wide applicability of PDMS to tissue contact is due to its generally low toxicity and biocompatibility, which was investigated in a publication by Rowe, Spence and Bass in 1948[4] and continues to be extensively studied for general biomedical suitability and specific implant applications.[5,6] From the perspective of chemistry, the strength of the two oxygen and two carbon (methyl group) bonds per silicon atom gives the material thermal stability up to 400°C, allowing autoclave sterilization, and preventing chemical decomposition under most physiological conditions.[7] This inertness has a downside for some applications; PDMS tends to poorly facilitate protein and cell attachment, resulting in poor soft-tissue integration, a lack of skin sealing around percutaneous devices and localized foreign body response with subcutaneous implants.[8]

Titanium has been recognized as the material of choice for many implant applications, especially when contacting bone or to limit contact with nickel. More recently, it has been applied to osseointegrated trans-epithelial prosthetic fixation for dentistry and experimental limb attachment.[9] It is the presence of a spontaneous and self-regenerating passive oxide layer on titanium's surface that is primarily responsible for the corrosion resistance[10] and biointegrative properties of this metal.[11-13] Titanium oxide reduces local inflammatory responses,[14,15] lowers the presence of local reactive oxygen species,[16,17] and dynamically incorporates elements from surrounding tissues after implantation.[18,19] Because of the properties of this (and other) refractory metal oxides, the problem of aseptic osseointegration of medical devices is all but solved.

BIOINTRAFACE

John D. Jarrell, PhD

Polyether ether ketone (PEEK) is increasingly finding use in orthopaedic applications like spinal and trauma implants. PEEK has a good combination of formability, mechanical properties, biocompatibility and radio transparency, but lacks some of the bioactive and integrative properties identified with titanium-based implants. Here we explore the use of metal-organic derived, hybrid coatings, as a means of creating antimicrobial treated PEEK biomaterials with a titanium oxide surface interface.

BIOMATERIALS AND BIOFILMS

While biomaterials like titanium, stainless steels, cobalt chrome, polyether ether ketone (PEEK), silicone and polyvinyl chloride (PVC) have been widely used for medical devices, catheters and implants, none of these materials provide active resistance to bacterial infection or prevents biofilm formation. Biofilm formation is a five-step process involving reversible attachment, irreversible attachment, maturation I, maturation II and dispersion.[1,2] Identification of the mechanisms at work in each of these steps has aided investigators in developing targeted approaches.[1-3] These include prevention of bacterial attachment, encouraging release,

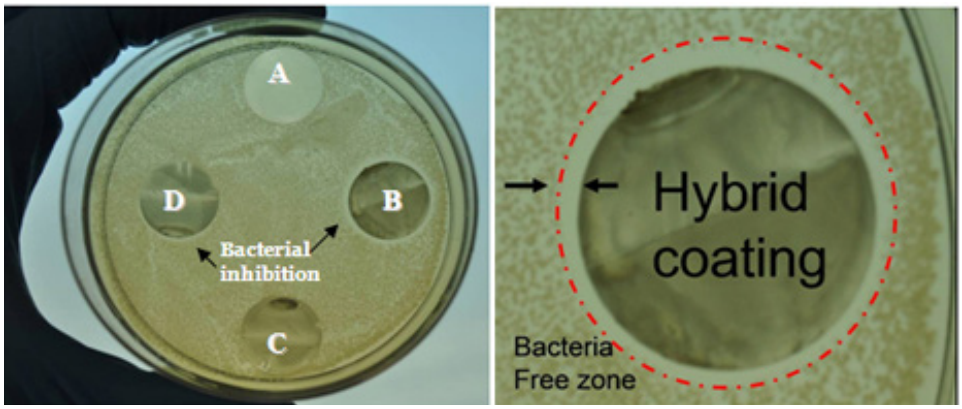

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Figure 1. In vitro results with glass discs with no coating (A), Hybrid #1 coating (B), amorphous Titanium Dioxide only (C), and Hybrid #2 coating (D) incubated in Petri dish with E. Coli-coated agar. Note large zone of bacterial inhibition surrounding disc coated with Hybrid #1 and smaller zone surrounding disc coated with Hybrid #2 (arrows). Right image is a close up view of bacteria free zone around Hybrid #1.

Hybrid coatings

BI's coatings are based on a new hybrid materials technology using metal-organic precursors to create both metal oxide and polymer coatings from liquid solutions. Each component of the coating is already in common use in other medical devices. The prospective coatings are optimized using an innovative rapid screening cell culture platform, inspired by the approaches used by large pharmaceutical companies for new drug discovery.

These promising in vitro results (Figure 1) have been followed by several small animal studies conducted at both Brown University and Rhode Island Hospital. Early applications that have been considered include catheters, fracture fixation devices, and transcutaneous osseointegrative devices (bone-anchored prosthetics for limb replacement).

disrupting quorum sensing and dispersion of the biofilm layer.[1,2] Another approach has been coined as "the race for the interface." That is, there is a competition for implant surfaces between healthy cells/tissues and bacteria. It has also been recently recommended that at least two approaches be employed to prevent bacterial formations on implants and overcome bacterial mechanism of resistance. The Food and Drug Administration (FDA) regulatory requirements and market forces must be taken into consideration in the development of a sensible and commercially feasible approach, which also holds potential for reducing overall healthcare costs. To be clinically relevant, an approach needs to meet at least three criteria: a clinically relevant, 2+ log reduction in bacterial growth, no prevention of tissue healing and no promotion of antibiotic resistance.

FIGHTING INFECTION

Several types of surface treatments have been investigated to reduce bacterial growth and infection, including: the introduction of nano surface topography, manipulation of surface chemistry and the permanent attachment of antibiotic drugs to implants to inhibit bacterial attachment, growth and resulting biofilm formation. Nano surface modifications are well-developed and have been demonstrated to facilitate healing and reduce the growth of bacteria, but not at the log scale level.[1] University of Pennsylvania researchers developed methods for permanently attaching antibiotic drugs to medical devices with good in vitro results against bacteria,[2] but raise the concern of preferentially selecting and encouraging development of drug resistant bacterial infections. Due to the recent increased number of antibiotic resistant bacteria, silver has been studied extensively as an alternative to antibiotics. Silver ion delivery has a history of use on medical devices, does not contribute to drug resistance and provides broad spectrum antimicrobial protection against gram-positive and gram-negative bacteria by at least six different mechanisms.[3-8] Bactericidal effects of silver depend greatly on concentration, particle size and shape in the case of silver particles. Exposure to silver causes changes in bacteria cell membrane morphology, and damage to intracellular proteins and DNA, which affect cell metabolism, cell division, and can result in cell death.

BIOACTIVE AND ANTIMICROBIAL COATINGS

Research conducted at Brown University, Rhode Island Hospital and in collaboration with the U.S. Department of Veterans Affairs shows that metal oxide and polymer hybrid surface treatments have the ability to prevent bacterial attachment and eliminate bacterial growth on the log-scale, while promoting healthy cell growth.[4-7] These coatings are based on a new hybrid-materials technology using metal-organic precursors to create both metal oxide and polymer matrix coatings from liquid solutions. Each component of the coating is already in common use in other medical devices. The prospective coatings are optimized using an innovative rapid screening cell culture platform, inspired by the approaches used by pharmaceutical companies for new drug discovery. Promising in vitro results have been followed by several small and large animal studies conducted at both Brown University and Rhode Island Hospital and third-party in vitro ISO biocompatibility testing and AATCC antimicrobial testing. The coating matrices have novel electro-chemical and controlled release properties to deliver bioactive agents, including metal ions like silver. The main advantages of these treatments over competitive delivery technologies is the ability to control the silver release properties and balance them with the bioactive properties of titanium oxide, the economical methods of application and the formation of a chemical bond between the treatment and the surface of the medical device.

BIOINTRAFACE®, THE COMPANY

BioIntraface®, Inc. (BI), was formed in February of 2009 to commercialize the biomaterials surface treatment technologies. The platform technologies involve the creation of economical, multifunctional metal oxide and polymer materials and coatings to control the bioactivity and antimicrobial properties of medical devices and implants. In 2009, the BI team won the Rhode Island Business Plan Competition, which was followed in 2010 by a Rhode Island Innovation Award in the category of Health Care & Biotechnology Innovations. In 2011, BI was issued two U.S. patents from their original filings and their first international patent claims were allowed in Australia and Mexico, with additional applications pending in the United States, the European Union and six additional industrialized nations. BI has continued optimizing and validating coatings for promising applications in orthopedics, dentistry, catheters, wound dressings, topical antimicrobial products, and cosmetics applications. It has also obtained third-party verification of ISO biocompatibility testing for eight coatings with increasing levels of antimicrobial agents, where no cytotoxicity was indicated and similar tests showing long lasting antimicrobial efficacy against multiple strains of bacteria. On the strength of this technology, BI is raising additional funding to launch multiple companies focused on specific antimicrobial products lines. In 2011, the establishment registered with the FDA as an initial importer of medical devices and plans to begin to obtain FDA approval for upgraded revision of specific device lines for distribution into the United States, Germany, France and the United Kingdom once adequate funding is obtained.

The initial management objective has been to create the infrastructure to warehouse and distribute branded devices into markets ready for a high-value line of antimicrobial devices and implants, while adding in-house manufacturing, quality and R&D capacity. In 2012, BI moved into a pilot manufacturing facility at Quonset to expand processes and research capacity to facilitate rapid growth and a robust new product pipeline.

LEADERSHIP

BI management is led by **John D. Jarrell, PhD, PE**, who is president and founder, with 25 years of experience in failure analysis and product liability of medical devices.

Christopher T. Born, MD, FAAOS, FACS, professor of orthopaedics at Brown University, is head of the BI Clinical Advisory and Chief Technical Officer (CTO).

Brown University Associate Professor of Medical Science and Engineering **Jeffrey Morgan, PhD**, is a co-founder and head of the Scientific Advisory Board. For more information: www.biointraface.com.

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