Montana State University
Center for Biofilm Engineering
Bozeman, Montana

Anti-Biofilm Technologies: Pathways to Product Development

College Park, Maryland
FEBRUARY 11, 2015

Proceedings

abstracts

Table of Contents

Presentation ToC

Presentation Abstracts

SESSION 1: Surface Disinfection Technologies

Development and assessment of test methods for antimicrobial products: Emphasis on biofilm methods

Presenter: ***Stephen Tomasino, PhD***, Senior Science Advisor, Office of Pesticide Programs
Affiliation: U.S. Environmental Protection Agency, Fort Meade, MD, USA

To meet the regulatory challenges associated with an ever changing marketplace—novel product claims, new infection control practices, and the emergence of new clinical pathogens—the EPA is systematically developing and assessing new quantitative efficacy methods, including those for testing biofilm claims. The involvement of standard setting organizations in assessing the clarity and technical quality of a method, in combination with conducting collaborative studies designed to evaluate method performance, is highly beneficial. The purpose of this presentation is to describe EPA's approach and assessment of test methods for antimicrobial products with an emphasis on biofilm test methods.

EPA's regulatory perspective on biofilms claims

Presenter: ***Marc Rindal***, Microbiologist, Antimicrobials Division
Affiliation: U.S. Environmental Protection Agency, Arlington, VA, USA

The Antimicrobials Division (AD) is responsible for all regulatory activities associated with antimicrobial pesticides, including product registrations. A brief overview seeking to relate biofilm efficacy label claims, test method performance, and submission requirements will be presented. Emphasis will be placed on test methods being supported, data requirements, and the impact of method modifications. Guidance examples will be provided.

Quantitative microbial risk assessment (QMRA) for hard surface disinfectants

Presenter: ***Michael Ryan, PhD***, Assistant Teaching Professor of Civil, Architectural & Environmental Engineering
Affiliation: Drexel University, Philadelphia, PA, USA

Cleaning and disinfecting are approaches used to reduce risks associated with disease transmission attributed to contaminated fomites. Quantitative microbial risk assessment (QMRA) provides a mechanism to develop technically informed disinfection goals for surface hygiene and safety. The bacterial levels used in current test methods for evaluating the efficacy of hard surface cleaners were developed with limited knowledge of the numbers and types of organisms that can be found on different surfaces. The goal of this study was to address a risk-based process for choosing the $\log_{10}$ reduction recommendations in contrast to the current EPA requirements. This analysis suggests that a 99% reduction in bacteria will most often reduce risk of infection from a single contact with fomites under general circumstances to levels of 10^{-6} as a measure of safety. The level of buffer provided 3–7 log reductions as specified by EPA's categories for disinfection ranged from 8 to 10,000,000 times more safety compared to what would be needed to achieve a 10^{-6} risk under normal circumstances. Future research is needed to refine these types of QMRA, including scenarios comparing key venues and after-events that cause high surface contamination.

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Agricultural applications of anti-biofilm compounds

Presenter: ***Christian Melander***, ***PhD***, Howard J. Schaeffer Distinguished Professor, University Faculty Scholar, Chemistry
Affiliation: North Carolina State University, Raleigh, NC, USA

Outside of their impact on human health and traditional industrial settings, bacterial biofilms can potentially play key roles in the pathogenesis of plant-based infections. We investigated the potential of imidazole-based anti-biofilm agents to serve as adjuvants to copper-based microbicides and we established that addition of the anti-biofilm compounds significantly augmented the ability of copper to control bacterial disease both in the greenhouse and in the field. These results inspired us to investigate the ability of simple, anti-biofilm natural products to prevent food spoilage of commercial crops, and again we established that anti-biofilm compounds effectively controlled bacterial infection.

Biofilm removal

Presenter: ***Philip S. Stewart, PhD***, CBE Director and Professor of Chemical & Biological Engineering
Affiliation: Center for Biofilm Engineering, Montana State University, Bozeman, MT, USA

Antimicrobial technologies have historically focused on killing microorganisms. In a biofilm system, it may be desirable to deploy technologies that remove biofilm. This presentation examines the process of biofilm removal and how it is distinct from the process of disinfection. Video microscopy of biofilms in flow cells reveals that many conventional antimicrobial agents fail to remove biofilm even when they cause substantial killing. In contrast, alternative chemistries are being developed that can weaken and remove biofilm without necessarily killing cells. Methods for assessing biofilm removal, and the importance of taking biofilm removal into consideration when interpreting other biofilm assays, will be discussed.

SESSION 2: Medical Device Technologies

Biofilms and public health

Presenter: ***LCDR K. Scott Phillips***, ***PhD***, ***USPHS***, Regulatory Research Scientist, Center for Devices & Radiological Health
Laboratory of Microbiology and Infection Control (LMIC)
Division of Biology, Chemistry and Materials Science (DBCMS)
Office of Science and Engineering Laboratories (OSEL)
Center for Devices and Radiological Health (CDRH)
Office of Medical Products and Tobacco (OMPT)
Affiliation: U.S. Food and Drug Administration (FDA), Silver Springs, MD, USA

The paradigm shift from thinking about bacteria as planktonic organisms to thinking about them in biofilm communities has significant implications for public health. The development of anti-biofilm technologies is an important scientific area of discovery in response to the increasing understanding of the role of biofilm in healthcare-associated infections. Because of the expense of clinical trials, reliable *in vitro* and *in vivo* test methods are needed to evaluate the effectiveness of anti-biofilm technologies. While creative and promising new technologies are being developed, it is crucial to develop a regulatory science framework for understanding the biological and molecular mechanisms responsible for how these technologies may impact clinical outcomes. This talk discusses unique aspects of biofilm pathophysiology and the public health impact of device-associated infections, followed by an introduction to anti-biofilm technologies and an analysis of current literature on test methods with *in*

Presentation ToC

vivo in vitro correlations (IVIVC). The outcomes of a recent workshop on the issue will be summarized and areas where further research is needed will be highlighted.

Antimicrobial-containing medical devices: A perspective

Presenter: ***Kapil Panguluri, PhD,*** Microbiologist/Team Leader, Center for Devices & Radiological Health
Affiliation: U.S. Food and Drug Administration (FDA), Silver Springs, MD, USA

FDA/CDRH regulates medical devices containing antimicrobial agents and combination products that contain antimicrobial drugs when the primary mode of action is that of a device. Recently there has been increased interest in adding antimicrobial agents to medical devices and to seek intended claims such as reduction or prevention of a device-related infection, or reduction or inhibition of colonization of a medical device. FDA's presentation will provide a perspective on this issue.

Research challenges for clinical translation of antimicrobial device technologies

Presenter: ***David W. Grainger, PhD,*** Professor of Pharmaceutics & Pharmaceutical Chemistry and of Bioengineering Health Sciences
Affiliation: University of Utah, Salt Lake City, UT, USA

Numbers of medical devices implanted annually are increasing, and with this, numbers of device-related infections increase as well. Infection remains an unresolved clinical problem across different device classes in different implant scenarios. The biofilm problem associated with perioperative surgical contamination and pathogen-device colonization remains formidable. Many types of materials designs and antimicrobial approaches continue to be levied against this problem, for both infection prophylaxis and infection therapy. The increased use of implantable materials and increasing incidence of antibiotic resistant infection makes this problem compelling. Many different approaches have been historically used to counter device-related infection including antibiotic lavages, locally tethered or released antimicrobials, device coatings, local electric fields and current applications, and newer approaches targeting bacterial adhesion mechanisms, communication pathways, and virulence factors.

Combination medical devices provide new innovative opportunities by allowing local antibiotic formulations to be released from established classes of implants. Few strategies to date have shown much efficacy *in vivo* in humans despite promising *in vitro* antimicrobial efficacy and even some translation to animal implant models. Scientific issues involve inadequate evaluation methods, including problematic, non-predictive *in vitro* assays and also irrelevant animal models of infection with devices. Development of new anti-infective medical devices requires a validated preclinical testing protocol. Preclinical infection assays predictive of ultimate clinical efficacy should serve as a control point for effective translation of new technologies to clinical applications; however, reliable validation of experimental and preclinical antimicrobial methodologies currently suffers from a variety of technical limitations. These include: the lack of agreement or standardization of experimental protocols; a general lack of correlation between *in vitro* and *in vivo* preclinical results; and lack of validation between *in vivo* preclinical implant infection models and clinical (human) results. Clinically, translation to humans is stymied by the formidable costs of conducting clinical trials.

Moriarty TF, Richards G, Grainger DW. "Challenges in linking preclinical anti-microbial research strategies with clinical outcomes for device-associated infections," *Eur Cells Mater* 2014;28:112–128.

Busscher HJ, van der Mei HC, Subbiahdoss G, Jutte PC, van den Dungen JJAM, Zaat SAJ, Schultz MJ, Grainger DW. "Biomaterial-associated infection: Locating the finish line in the race for the surface," *Sci Transl Med* 2012;4:153rv10.

Presentation ToC

Grainger DW, van der Mei HC, Jutte PC, van den Dungen JJAM, Schultz MJ, van der Laan BFAM, Zaat SAJ, Busscher HJ. "Critical factors in the translation of improved antimicrobial strategies for medical implants and devices," *Biomaterials*, 2013;34(37):9237–43.

Everything SLIPS: No bacteria left behind

Presenter: ***Caitlin Howell***, ***PhD***, Technology Development Fellow, Wyss Institute for Biologically Inspired Engineering
Affiliation: Harvard University, Cambridge, MA, USA

Learning from and mastering Nature's concepts promises to drive a paradigm shift in modern materials science and technology. Based on this philosophy, our group has recently developed ultra-slippery, pressure stable surfaces through inspiration from the *Nepenthes* pitcher plant. These Slippery Lubricant-Infused Porous Surfaces, or SLIPS, use an immobilized liquid layer to present a "moving target" for bacterial adhesion and have shown promise as biofilm-resistant coatings. Static assays against clinically relevant bacteria such as *E. coli, S. aureus, S. epidermidis*, and *P. aeruginosa* have shown drastic decreases in adherent bacteria and nearly no biofilm formation compared to untreated controls, all without toxic effects. Assays under flow conditions in catheter analogs showed similar results. Furthermore, we have developed a way to modify SLIPS to include a self-replenishing system which can significantly increase their longevity. We anticipate that these materials will prove useful in controlling biofilm formation in a wide range of applications.

Methods for assessing biofilm prevention

Presenter: ***Darla Goeres, PhD***, Manager, Standardized Biofilm Methods Laboratory
Affiliation: Center for Biofilm Engineering, Montana State University, Bozeman, MT, USA

In the battle to reduce medical device and implant related infections, prevention of bacterial colonization is a logical strategy. Bacterial colonization of a surface is a precursor to biofilm formation, the etiological agent of many implant and device related infections. One approach is to design medical devices with antimicrobial properties. This presentation will provide an overview of the desirable attributes of an *in vitro* method used to quantitatively evaluate the prevention of bacterial colonization on a Foley catheter. In addition, the presentation will include an overview of the published methods used to assess the prevention and/or reduction of biofilm growth on Foley catheters. Through this presentation, CBE hopes to initiate a discussion between the stakeholders and regulatory agencies on the significance of *in vitro* methods for testing antimicrobial medical devices.

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