NEW BIOGUARD™ ANTIMICROBIAL WOUND DRESSING WITH ADVANCED NIMBUS® TECHNOLOGY

Bernd Liesenfeld[1]*, David Moore[1], Albina Mikhaylova[1], Jillian Vella[1], William Toreki[1], Gregory Schultz[1,2],
[1]Quick-Med Technologies, [2]University of Florida, *corresponding author

2010 WOUND HEALING SOCIETY CONFERENCE

Abstract

FDA has recently cleared the novel BIOGUARD antimicrobial dressing featuring a permanently bound microbicide that provides long lasting microbial suppression in the dressing, generating an effective barrier to the transmission of pathogens. This technology assures the safest possible wound bed environment, and incorporates several features to prevent bacteria from becoming resistant. BIOGUARD dressings were shown to be effective against common wound pathogens, and demonstrate the highest possible level of biosafety, by standard ISO biosafety tests, and by rigorous testing in mammalian cell models. The polymeric bound antimicrobial was shown through testing to induce no bacterial resistance. This novel combination of efficacy and safety offers a new cost-effective choice for caregivers to provide their patients with a barrier dressing suitable for prophylactic measures against nosocomial infections.

Background

The dangers of bacterial colonization in wounds are well understood by caregivers – particularly because compromised surfaces are the primary point of vulnerability for the patient. BIOGUARD antimicrobial barrier dressing optimizes efficacy and safety to provide caregivers the ability to safely apply the dressings prophylactically to help prevent pathogen transfer. Other currently available antimicrobial dressings are designed to aggressively treat colonized wounds (see section on Zone of Inhibition and Figure 2) by leaching antimicrobial agents into the wound bed. This approach is successful in reducing wound colonization, but released small antimicrobial molecules may select for bacterial resistance, cause skin discoloration / reaction, or impede wound healing (Wang et al, 2009; Silver et al, 2003; Van Den Plas et al, 2008). Additionally, the cost of many current antimicrobial dressings keeps them out of reach of many patient populations for regular use. BIOGUARD dressings were designed to provide an antimicrobial barrier technology that is effective, economical, and safe enough for broad application.

Mechanism of Antimicrobial Activity

The BIOGUARD antimicrobial barrier dressing is based on the patented NIMBUS® technology (Quick-Med Technologies, Inc.). The active antimicrobial agent is permanently bound to the dressing surface, and acts on the wound pathogen by physically disrupting the prokaryotic cell wall. Electron micrographs (**Figure 1**) show *Escherichia coli* cells before and after contact with a polymeric quaternary microbicidal agent. The left panel shows healthy intact cells, while the right panel shows disrupted and lysed cells–deflated membrane sacs with their intracellular contents released. This process does not rely on the agent entering the cell: the physical size of the polymeric antimicrobial precludes entry into the cell, even if the polymer were not permanently bound to a solid surface. Lysis of the cells is induced from outside, preventing bacterial cells from being able to generate resistance to the antimicrobial polymer, as all known acquired resistance mechanisms are cellular adaptations to small internalized agents – either through efflux mechanisms or re-routing of metabolic pathways (Poole, 2002).

The macromolecular agent responsible for this mode of action is poly(diallyldimethylammonium chloride), or polyDADMAC, a cationic quaternary ammonium polymer. Polycationic agents combine broad-spectrum antibacterial activity with relatively low toxicity allow, allowing use of in contact lens cleaning solutions (Hibbard, 2005), topical antimicrobial preparations (Kramer et al, 2004; Daeschlein et al, 2007) and in wound dressings (Lee et al, 2004). The most similar molecule currently used in wound dressings is PHMB (PolyHexaMethylene Biguanide); the main important difference being that the polyDADMAC molecule is approximately 100 times larger. Literature reports that molecular size is important because the level of toxicity to eukaryotic cells induced by cationic biocides is inversely related to the size of the molecular chain (Ikeda, 1991; Gilbert and Moore, 2005).

Testing Summary

Test Type	Test Method	Result for Bioguard
Antimicrobial Efficacy	AATCC method 100-1998: "Antibacterial Finishes on Textile Materials, Assessment of."	Strong antimicrobial efficacy (>99.99% for common wound pathogens, see table at right for more data).
Cytoxicity	Agar diffusion overlay method, as per ASTM F895-84	Lowest Cytotoxicity score possible in test. Non-cytotoxic per test evaluation
Cytoxicity	Direct contact method with L929 cell line, per ASTM F813-07	Judged non-cytotoxic per test evaluation.
Dermal Irritation	Primary Skin Irritation as per ISO 10993-10 guidelines	Lowest Irritation score possible in test: evaluated as Negligible Irritant
Dermal Sensitization	Repeated Patch Derma Sensitization per Buehler Method.	Lowest Sensitization score possible in test: evaluated was no sensitization observed.
Zone of Inhibition	Inhibition test on *E. Coli* plate	No growth on or under dressing, no visible inhibition away from dressing surface.
Bacterial Resistance	Antimicrobial efficacy of step-wise adapted survivor cultures	Antimicrobial efficacy of the BIOGUARD dressing did not change over 10 iterations of step-wise adapted cultures
Bacterial Resistance	Minimum Inhibitory Concentration (MIC) of step-wise adapted survivor cultures	MIC of BIOGUARD active for *E. Coli* did not change over 10 iterations of step-wise adapted cultures.

Zone of Inhibition.

The BIOGUARD dressing is different from other antimicrobial dressings in that it does not have a zone of inhibition (**Figure 2**). The bound antimicrobial protects the dressing without leaching any chemical agents into the wound bed, and therefore nothing cytotoxic that could retard healing enters the wound bed. Also, the absence of a leached agent ensures the absolute minimum possibility for bacteria to develop resistant strains.

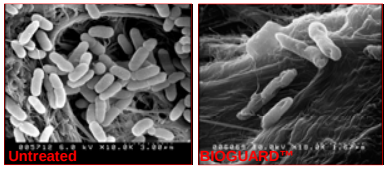

Figure 1 (left). Scanning Electron microscope images of *E. coli* on untreated gauze wound dressing and on BIOGUARD wound dressing (as labeled). *E. coli* bacteria grown in contact with control substrate had intact membranes and full rod shapes. *E. coli* exposed to BIOGUARD surfaces show clear membrane damage and altered general morphology. Some bacteria show small holes and indentations indicative of cellular envelope damage.

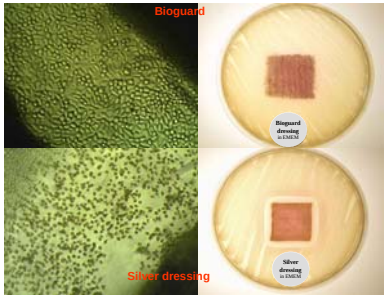

Figure 2 (left). Direct contact cytotoxicity tests and zone of inhibition plates (*E. coli*) for BIOGUARD and for a silver dressing. BIOGUARD (top) shows no zone of inhibition, and direct contact testing with L929 fibroblast cell line shows normal healthy growing cells. The silver dressing shows a zone of inhibition where the chemical leaches out of the dressings: the effect of leached silver is shown in the direct contact assay by malformed and depopulated cells.

Antimicrobial Testing

Wound pathogen	ATCC number of species	Average % kill vs. untreated control, t=0	Average % kill vs. untreated control, overnight
Staphylococcus aureus	ATCC 6538	99.9995%	99.999992%
MRSA *(Methicillin resistant S. aureus)*	ATCC BAA-44	99.9996%	99.999998%
Staphylococcus epidermis	ATCC 12228	99.9995%	99.999997%
Pseudomonas aeruginosa	ATCC 15442	99.988%	99.99999%
Enterococcus faecium	ATCC 19434	99.9996%	99.999987%
Escherichia coli	ATCC 8937	99.9996%	99.999997%
Escherichia coli	ATCC 15597	99.9996%	99.999998%
Acinetobacter baumannii	ATCC 19606	99.9989%	99.999999%
VRE (Vancomycin resistant *Enterococcus faecium*)	ATCC 51299	99.9996%	99.999991%

Safety and Biocompatibility

BIOGUARD dressings were exhaustively tested for safety and biocompatibility. Direct dermal testing included skin irritation and sensitization, showing no irritation or sensitization. Sensitive in vitro models were used to assess cytotoxicity by multiple methods, including not only agar diffusion but also direct contact testing on fibroblast cell lines, showing that BIOGUARD impeded cellular growth no more than negative controls, while a silver dressing showed significant cytotoxicity in the same assay. Testing of step-wise adaption for 10 iterations showed that bacteria did not increase resistance to the BIOGUARD dressing.

Conclusions

The BIOGUARD dressing demonstrated high efficacy against common wound pathogens, while maintaining the highest possible level of biosafety. This is most clearly illustrated by Zone of Inhibition testing: the lack an inhibitory zone confirms that BIOGUARD antimicrobial barrier dressing is able to control pathogens in the dressing without exerting a physiological effect on the wound bed. A silver dressing tested alongside showed a zone of inhibition, and retardation of cell growth in mammalian cell models. Since the BIOGUARD antimicrobial barrier dressing is shown to be able to fulfill its protective function without impeding wound healing, and without causing concern over bacterial resistance it is safe enough to be used broadly as a prophylactic device to protect vulnerable patients and wounds from infection without adding risks for the patient.

References

•*Daeschlein G, et al.* Feasibility and clinical applicability of polihexanide for treatment of second-degree burn wounds. Skin Pharmacol Physiol. 2007;20(6):292-6
•*Gilbert P and Moore LE*, Cationic Antiseptics: diversity of action under a common epithet, J Appl Microbiol., 2005, 99(4):703-15.
•*Hibbard JS* Analyses comparing the antimicrobial activity and safety of current antiseptic agents: a review. J Infus Nurs. 2005 May-Jun;28(3):194-207
•*Ikeda, T.* Antibacterial activity of polycationic biocides. High Perform. Biomater. 1991; 7: 743-764.
•*Lee WR, et al.* In vitro efficacy of a polyhexamethylene biguanide-impregnated gauze dressing against bacteria found in veterinary patients. Vet Surg. 2004 Jul-Aug;33(4):404-11.
•*Poole K*, Mechanism of Bacterial Biocide and Antibiotic Resistance, *Journal of Applied Microbiology*, 2002:92 Suppl.:55S-64S
•*Silver S.* Bacterial silver resistance: molecular biology and uses and misuses of silver compounds. *FEMS Microbiology Reviews.* 2003; 27:341-353.
•*Van Den Plas D, et al.* Differential cell death programmes induced by silver dressings in vitro. Eur J Dermatol. 2008 Jul-Aug;18(4):416-21
•*Wang XQ, et al.* Silver deposits in cutaneous burn scar tissue is a common phenomenon following application of a silver dressing. J Cutan Pathol. 2009 Jul;36(7):788-92

WWW.QUICKMEDTECH.COM

Roy Carr – Director of Business Development, Medical Devices
Email: rcarr@quickmedtech.com (561) 771-1306
Gerald M. Olderman - Ph.D. VP, Research & Development
Email: jolderman@quickmedtech.com (561) 771-1304