DEVELOPMENT AND IMPLEMENTATION OF AN ANTIMICROBIAL BARRIER WOUND DRESSING OPTIMIZED FOR PROPHYLACTIC USE

Albina Mikhaylova[1*], Bernd Liesenfeld[1], David Moore[1], Jillian Vella[1], William Toreki[1], Robert Nappo[2], Janet Popp[2], Lisa Youngblood[2], David Mozingo[3], Tera Thigpin[3], Gregory Schultz[1,3]

[1]Quick-Med Technologies, [2]Shands at the University of Florida, [3]University of Florida, *corresponding author

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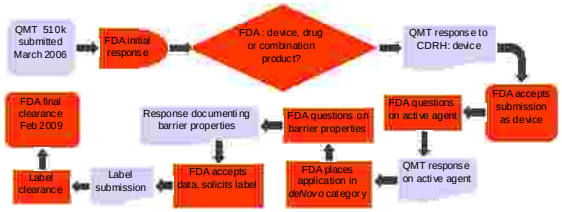
Abstract

The novel BIOGUARD™ antimicrobial dressing was developed by Quick-Med Technologies in cooperation with various UF affiliated staff, alumnae and cooperating facilities. We present technical details of note, and detail major milestones from the conception of the technology to clinical validation of the final commercial product. The translation of technology from the laboratory to regulatory clearance can be a long and arduous process, but is only the first in the series of steps that takes a laborat finding from nascent technology to commercial product. We detail some of the major of steps undertaken in our own translation from technology to product. Ultimately the only meaningful test of a medical product is in being able o provide benefits to the patient first and foremost, and to healthcare providers and facilities as a consequence. In terms of specific application, the BIOGUARD dressing line was designed with patient safety as the foremost consideration, with the aim of providing an antimicrobial chemistry that is suitable for prophylactic implementation. Clinical observations on implementation are provided.

Regulatory Aspects

The regulatory clearance process for a new antimicrobi echnology can be a long and complicated pathway, as is illustrated in the flow-chart below. This chart details some of the major ste the submission process, but is by no means exhaustive.



Mechanism of Antimicrobial Activity

The BIOGUARD antimicrobial barrier dressing is based o 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. The macromolecular agent responsible for this mode of action is poly(diallyldimethylammonium chloride), or polyDADMAC, a cationic quaternary ammonium polymer. Gilbert and Moore (2005) describe the mechanism of cell wall disruption induced by polymeric cationic biocides in excellent detail as shown graphically in **Figure 1**. The cationic polymer chains coordinate to the anionic segments of the phospholipid membrane, displacing stabilizing calcium ions. As increasing numbers of cell membrane molecules coordinate to the polymer, the integrity of e bacterial membrane is compromised, leading to gaps and holes as shown in the image.

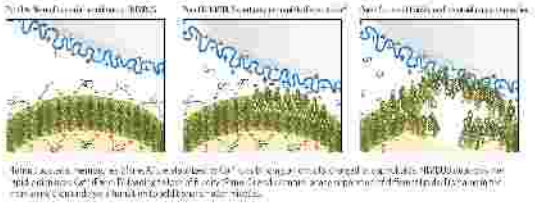


Figure 1: Conceptual Representation: action of polymer cationic biocidal agent

The theoretical representation is supported by electron micrographs (**Figure 2 on the right**), which 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 (Mikhaylova et al, 2010).

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)
Cytotoxicity	Agar diffusion overlay method, as per **ASTM F895-84**	Lowest Cytotoxicity score possible in test. Non-cytotoxic per test evaluation
Cytotoxicity	Direct contact method with L929 cell line, per **ASTM F813-07**	Judged non-cytotoxic per test evaluation
Dermal Irritation and Sensitization	Primary Skin Irritation and Sensitization (Buehler method) as per **ISO 10993-09** guidelines	Lowest Irritation and Sensitization score possible in test
Zone of Inhibition	Inhibition test on *E. Coli* plate	No growth on or under dressing, no visible inhibition away from dressing surface
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

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%
Acinetobacter baumannii	ATCC 19606	99.9989%	99.999999%
VRE (Vancomycin resistant *Enterococcus faecium*)	ATCC 51299	99.9996%	99.999991%

Zone of Inhibition.

The BIOGUARD dressing is different from other antimicrobial dressings in that it does not have a zone of inhibition (**Figure 3, below**). BIOGUARD (top row) 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 hed silver is shown in the direct contact assay by malformed and depopulated cells.

The bound antimicrobial protects the dressing without eaching any chemical agents into the wound bed, and therefore nothing cytotoxic that could retard healing ers the wound bed. Also, the absence of a leached agent ensures the absolute minimum possibility for bacteria develop resistant strains.

Figure 2 (above). 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 with exuding intracellular content.

Figure 3 (below). Direct contact cytotoxicity tests and zone of inhibition plates (*E. coli*) for BIOGUARD and for a silver dressing.

Clinical observations

Gauze bandages and pads are commonly used as dressings for patients with large wounds. However, a disadvantage of gauze bandages is the absorption of exudate into the dressing. Exudate absorption contributes to the development of high levels of bacteria in the dressing.

BIOGUARD, a new gauze with a bound antimicrobial polym was used instead of standard gauze bandages in the treatment of three patients. Two of these patients were suffering from Toxic Epidermal Necrolysis Syndrome (TENS) with epidermal involvement of approximately 90% total body ace area (TBSA). The third patient had full thickness thermal burns of greater than 70% TBSA.

Within 24 hours of applying standard gauze bandages to the wounds, the dressings developed a metallic green color and strong odor, characteristic of *Pseudomonas aeruginosa*. In marked contrast, BIOGUARD gauze bandages applied to the wounds adjacent to the standard gauze dressings, remained white with no visible evidence of bacteria fouling.

These initial clinical results suggest that BIOGUARD uze bandages may prevent rapid bacterial growth in gauze dressings saturated with heavy exudates. The reduction in bacteria could lead to a decrease in the contamination of open wounds, as compared to standard dressings. Additional benefits of using BIOGUARD gauze bandages may include reduced wound odor, frequency of dressing changes, and the spread of bacteria from fouled dressings to the patient and clinical personnel.

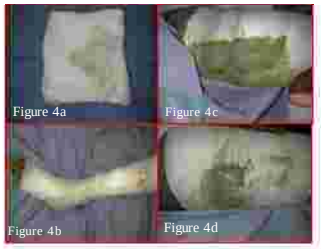


Figure 4a shows standard gauze bandages with exudate present from a donor site 24 hours after placement. The exudate is green metallic in color and has a foul odor present. **Figure 4b** shows a burn patient treated with BIOGUARD gauze bandages. It is evident that although there is a large amount of exudate present, it is not green in color and is odor free. **Figure 4c** is a Donor Site treated with standard gauze dressings that are metallic green in color and a strong odor is present. **Figure 4d** shows the same Donor Site after 24 hours of treatment with BIOGUARD gauze bandages. It is apparent that exudate is present but the color and odor have improved.

Conclusions

The BIOGUARD dressing demonstrated high microbicidal efficacy (~6-log kill) against common wound pathogens, while maintaining the highest possible level of biosafety in the laboratory testing. 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 sil dressing tested alongside showed a zone of inhibition, and retarded growth of cultured mouse fibroblasts.

Initial clinical observations at Shands Burn Center were very positive. Multiple experienced Burn Unit nurses noted reduction in exudate color and odor in patients treated with BIOGUARD as c pared to standard gauze dressings. Further clinical trials are being discussed to show ef y.

In summary, these *in vitro* data show that BIOGUARD dressing provides a highly eff ve antimicrobial barrier function without damaging cells that are essential for wound healing. Initial clinical experiences indicate that BIOGUARD dressing reduces bacterial bioburden in dressings on highly exudating wounds. Future clinical studies will compare bacterial levels in BIOGUARD dressing and standard gauze dressing and bioburden in wounds to assess the impact on infection and healing of wounds in vulnerable patients.

References

WWW.QUICKMEDTECH.COM

RoyCarr – 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