Procellera™

With PROSIT™ Technology

Scientific Summary

VOMARIS

SCIENTIFIC SUMMARY:
PROCELLERA™ with PROSIT®: A Novel Bioelectrical Dressing

Bioelectric Wound Healing

- FDA Cleared
- Proven Broad-Spectrum Antimicrobial Efficacy
- Bactericidal, Fungicidal
- Clinical Efficacy

PROCELLERA™ Antimicrobial Dressing is FDA cleared for professional use for partial and full-thickness wounds such as: pressure ulcers, venous ulcers, diabetic ulcers, burns, surgical incisions, and donor and/or recipient graft sites.

BACKGROUND

Prosit® technology consists of a matrix of biocompatible micro-cells and is designed to generate a sustained electrical microcurrent on the surface of a device. This technology is based on a unique biophysical mechanism of action resulting from low levels of electrical energy produced within the device. **Prosit®** has passed all tests for biocompatibility.

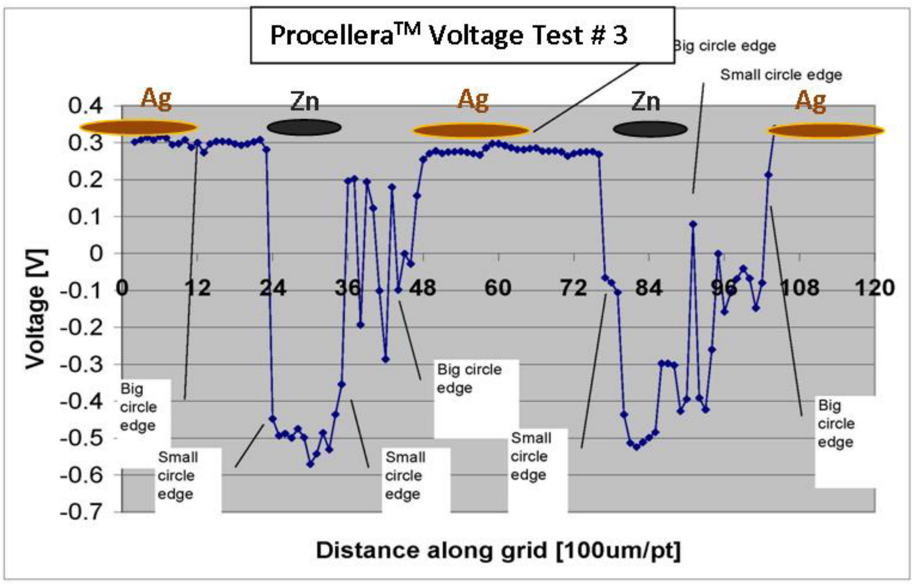
Its dressing form, **PROCELLERA™**, is self-contained, can be cut to fit as needed and requires no external power supply. The device provides an antimicrobial barrier to the wound site. In the presence of a conductive fluid, such as wound exudate or normal saline, the device activates to produce a sustained predetermined microcurrent similar to the microcurrent that occurs at areas of skin injury in normal hosts.

As documented extensively in the literature, this physiologic local microcurrent may be necessary for the initiation of wound healing and the transport of cells to the healing wound margins. Additionally, it is well established that antimicrobial action is augmented in the presence of a micro-charged field resulting from disruption of the charge characteristics inherent for specific microbes.

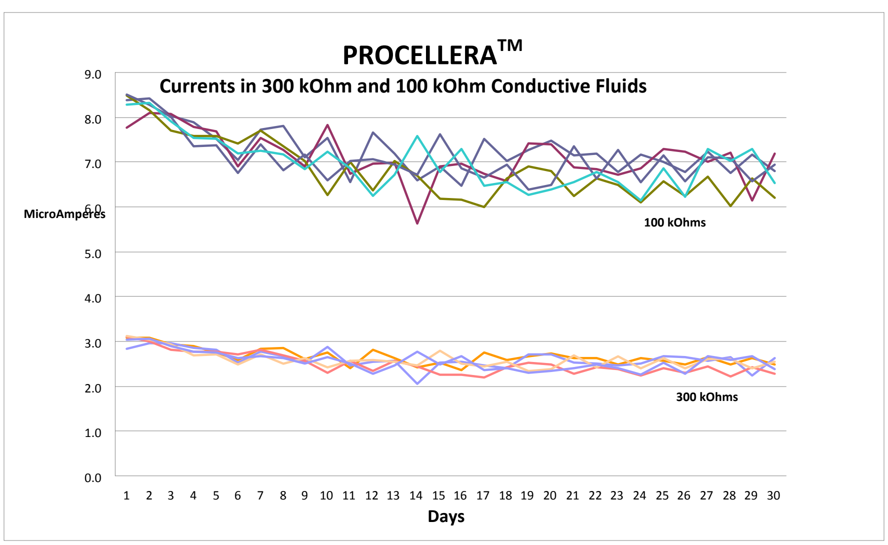
Reduced pain, faster healing, and improved scar appearance are the ultimate goals of successful wound healing. Clinical experience with **PROCELLERA™** has demonstrated profound effects on wounds. **PROCELLERA™** dressing should be used under a secondary dressing or bandage, which keeps it in place and helps maintain a moist wound environment.

SCIENTIFIC EVIDENCE

Electric stimulation as a means for wound healing has been recognized as safe and effective in many studies and has been used successfully to reduce risk of infection, decrease pain and inflammation, and enhance wound healing. Endogenous electrical activity is normally present between cells in mammalian skin. With skin injury, physiologic electrical activity is created by a differential in electro-chemistry between tissue layers and is generally confined to the wound edges where the current provides a transport mechanism for cells migration. This electrical signal is also essential to the cascade of reactions and processes required to achieve wound healing. Studies show that cells are transported along electrical current lines which are generated in wounds via a process called galvanotaxis. Fibroblasts, keratinocytes, neutrophils, and mast cells migrate in the presence of low level micro-currents. The addition of an external micro-current significantly enhances this process since the current is not constrained only to the perimeter of the wound but may also cover and affect the entire wound surface. In addition, pathogens such as bacteria, fungi, molds and yeast also are electrically influenced. Numerous studies have shown that external electric current is lethal to microbes, while providing a beneficial stimulus to wound healing in the host. The use of bioelectric dressings augments this antimicrobial process in addition to facilitating and enhancing wound healing.

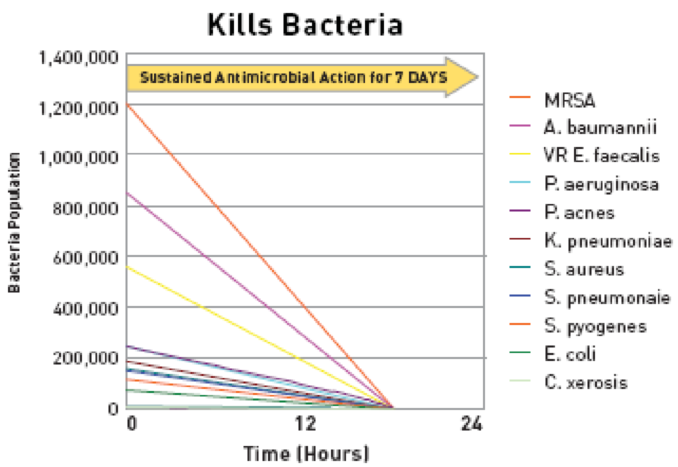


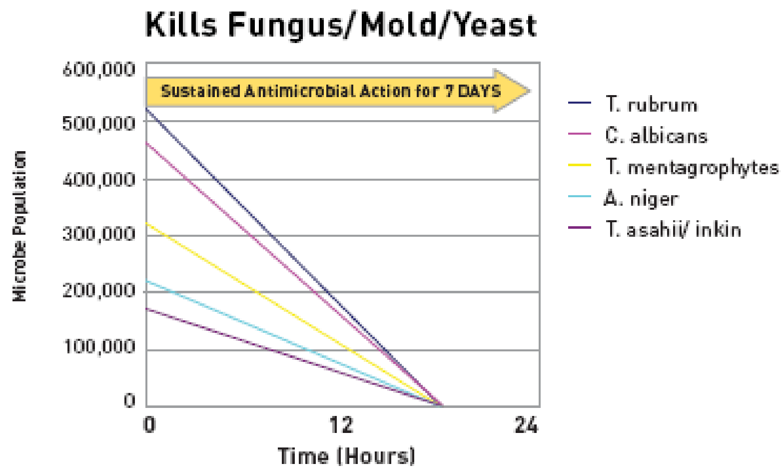
The figure shows a Bioelectric Field map of Prosit Technology using a high-impedance, gold-based micro-probe. When immersed in normal saline solution, the spatial electric field characteristics for Procellera, are observed. Note the net potential of 0.7 – 0.9 V between the Ag and Zn spots.



The figure shows the electrical microcurrent of 2.5 – 8.5 micro Amperes recorded over 30 days with the **Procellera™** device immersed in normal saline and Lactated Ringers. The ranges of the microcurrent as well as the measured impedances of the fluid are very similar to those reported *in vivo*.

The figures below show the attenuation of various bacterial and microbial species in the presence of **Procellera™** *in vitro*, using a standard test method (AATCC Test Method 100-1993).





Porcine In-Vivo Study: Improved Epithelialization and Favorable Wound Healing Response

Two porcine studies were conducted by the University of Miami's Miller School of Medicine Department of Dermatology in 2007 to evaluate the effects of bioelectric dressings on deep partial and full thickness cutaneous wounds (Davis et al. 2007, 2008) The bioelectric dressing significantly increased the degree and rate of wound epithelialization (p-value<0.001). Epithelial migration was enhanced, whereby, on day 5, 67% of wounds covered with a bioelectric dressing healed in contrast to only 20% of the control wounds. Histologic examination of the wounds revealed increased epithelial thickness, decreased eschar formation, and decreased neutrophil infiltration of the wounds treated with a bioelectric dressing in comparison to the control group.

Studies were completed to examine genetic markers present in the healing tissue. The following markers were examined: 1) The inflammatory cytokine interleukin-1α (IL-1α); 2) structural dermal collagen expression with COL-1, the main component of mammalian skin; and 3) COL-3, which is present in early phases of wound healing and typically replaced during wound maturation; 4) matrix metalloproteinase–9 (MMP-9), an extracellular protease. Early wound inflammation was reduced as indicated by down regulation of the levels of IL-1α in the case of the bioelectric dressing compared to the polyester control side. Further, the IL-1α expression peaked later in the case of the bioelectric dressing. These results are indicative of a delayed and suppressed inflammatory response with the bioelectric dressing. Reduced inflammation is associated with reduced pain and improved aesthetics in human wound healing.

Comparative analysis of matrix metalloproteinase (MMP-9), involved in degradation of the extracellular matrix proteins, was reduced in the bioelectric dressing treated group. Despite the complexity of ongoing processes during wound healing, the reduced expression of MMP-9 is potentially indicative of a better prognosis for chronic wound healing with the bioelectric dressing. For example, MMP-9 levels are increased in persistent non-healing ulcers with increased tissue breakdown and reduced ability of keratinocytes to adhere to the open wound beds.
Overall levels of COL–1 in late stage healing were down regulated in wounds treated with the bioelectric dressing. Expression of both, COL-1 and COL-3 was increased in the polyester dressing control, compared to the bioelectric dressing. The more persistent upregulaltion of COL-3 in the case of the polyester controls could be associated with lower wound strength and recurrent injury. Although expression of COL-1 is

indicative of normal adult reparative healing, persistent elevated late stage COL-1 is seen in hypertrophic scarring and keloid formation. Within the duration of the study, the bioelectric dressing treated wounds were assessed to attain a later stage of tissue remodeling compared to the controls.

Analysis of the data from the University of Miami Porcine Studies indicates that bioelectric dressing-treated wounds demonstrate significant improvement of epithelial migration than the controls. Further clinical studies are being conducted to confirm the statistical significance of the efficacy of the bioelectric dressing in regards to pain reduction, improved scarring and improved quality of wound strength and quality of life.

Davis SC, Gil J, Valdes J, Perez R, Rivas Y. Assessment of the effects on wound healing and gene expression of a bioelectric dressing using a porcine wound model and real time reverse transcriptase-polymerase chain reaction. J Am Acad Dermatol. 2009;60:AB200.

CLINICAL EVIDENCE

Clinical Study – Improved Healing and Reduced Pain Response following Cosmetic Laser Facial Resurfacing

An IRB-approved randomized pilot clinical study was conducted to determine the preliminary safety and efficacy of **Procellera™** when used to cover partial thickness burns after cosmetic laser resurfacing procedures. Twenty-seven patients underwent cosmetic facial resurfacing with a 2940 nm wavelength Er:YAG laser to ablate skin tissue up to a depth of 40 microns. The patients were randomized into two groups. The control group was treated with standard of care wound coverage which included a petrolatum-based ointment and silicone face masks. The active study group was treated using a **Procellera™** total face mask applied immediately after the procedure. Subjective pain levels were measured by utilization of a Visual Analog Scale. Signs of postoperative erythema, edema, and healing were evaluated visually by the investigators.

Results:

The control group healed in 9 days, while the treated group (**Procellera™** mask) healed in 4 days. This represented a healing improvement of 55% in the group treated with **Procellera™**.

Immediately after application of the **Procellera™** mask, there was a 74.1% reduction in subjective pain levels seen in the study group. All (100%) of the control group experienced pain levels high enough to require opiate-based analgesics. None of the **Procellera™** mask group required narcotics, needing only over the counter (OTC) analgesics. Among the **Procellera™** treatment arm, 77.8% required no medication at all. While not a focus of this study, it was observed that none of the **Procellera™** -treated group had any viral outbreaks. This observation is of relevance, since for approximately 10% of patients who undergo ablative cosmetic procedures, a herpes outbreak is expected.

Conclusions:

In this study, **Procellera™** reduced pain and demonstrated faster healing. Use of opiate-based analgesics was not required by any of the patients treated with **Procellera™**. No adverse events were reported nor observed by the investigator in this study.

Parker, I et al. The Treatment of Partial Thickness Burns with a Bioelectric Dressing Following Cosmetic Laser Facial Resurfacing. [abstract] J Burn Care Res 2009;30,2:AB171.

Cosmetic Laser Facial Resurfacing Study


Immediate Post-Resurfacing


Immediate Post-Resurfacing


4 Days Procellera™


3 Days Control Dressing + Ointment

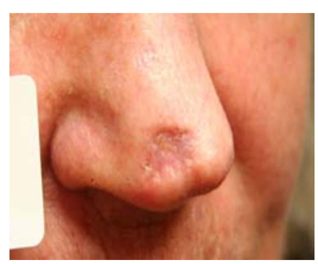
CLINICAL TRIALS AND CASE STUDIES:

Procellera™ has shown marked improvement in the healing of acute and chronic non-healing wounds as compared to current therapy modalities. Clinical data has been gathered during IRB-approved clinical trials (e.g., study comparing healing rates with **Procellera™** and other wound care dressings following electrodessication and curettage of skin lesions), as well as reported cases from the field. Working within wound care centers, physicians were asked for their most challenging cases. **Procellera™** has been observed to initiate healing in wounds that had failed all other methods of treatment. Many were scheduled for amputation. The case examples below are a sampling from a recent scientific poster presentation (Sheftel, 2008).

ACUTE WOUND

Patient Profile
Age/Gender: 67 year-old female
Diagnosis: Basal Cell Carcinoma

Wound Profile
Comments: Treated with Moh's surgery. Wound healing by secondary intention, prevented skin graft
Length of treatment: 4 weeks



ACUTE WOUND

Patient Profile
Age/Gender: 78 year-old male
Diagnosis: Skin lesion
Co-Morbidity: High cholesterol, HTN, thyroid

Wound Profile
Comments: Treated with curettage & electrodessication
Length of treatment: 3 weeks

CHRONIC WOUND

Patient Profile
Age/Gender: 82 year-old female
Diagnosis: Venous stasis ulcer
Wound Profile
Length of treatment: 4 weeks

The role of a bio-electric, antimicrobial dressing in the healing of acute and chronic wounds, S. N. Sheftel, Clinical Symposium on Advances in Skin and Wound Care, Las Vegas, 2008.

PATENTS:

US 7,457,667 Current producing surface for a wound dressing
US 7,662,176 Footwear apparatus and methods of manufacture and use
US 7,672,719 Batteries and methods of manufacture and use
Taiwan 1280142 Batteries and methods of manufacture and use

PCT Application 05723362.9 Batteries and methods of manufacture and use

Allowed June 2010 now pending:
US 20090062723 Current Producing Surface for Treating Biologic Tissue

Patents pending in Australia, Canada, Europe & Japan. Other patents applied for in the USA.

LITERATURE REVIEW:

Wound bioelectrical activity and potential has been identified and investigated for over 25 years. One of the initial clinical studies identified electrical activity within wounded tissue as illustrated by Illingsworth and Barker (1980) who measured current from 10 – 30 μA/cm2 surrounding the stump surface of an accidentally amputated finger. The concept of electrical wound activity was furthered by Alvarez et al. (1983) in which a silver-impregnated nylon electrode was placed into a wound bed in pig skin and applied 50 – 300 μA DC current. It was observed that wounds healed 29% faster compared to controls. His findings also suggested that migration and/or proliferation of fibroblasts were influenced by the electric field.

In earlier studies, (Barker et al., 1982 and Jaffe and Vanable, 1984), showed that a wound was found to produce about 1 microampere of current when immersed in saline. K.R. Robinson (1985) reported that the migration and/or orientation of cells can be controlled by imposing relatively modest electrical fields across them in vivo. Cells which are affected include epithelial cells, fibroblasts, macrophages, and leucocytes. Nannmark et al. 1985 showed the presence of an electrical field can cause an increase in capillary permeability to macromolecules and leucocytes as well as extravasation of white blood cells from the capillaries. Neither event was seen in non-stimulated controls.

Vanable (1989) concluded that the epidermis of the skin acts as a battery. This research documents that an endogenous electrical current at the site of injury is found to exist in the epidermis. In theory, this bioelectrical potential stimulates cell migration that must occur during healing. Vanable observed that the highest potential occurs in the first 0.5 mm of skin bordering the wound and that there is a voltage gradient in the vicinity of the wound. It was also noted that negligible current was present in dry wounds most likely due to high resistance in non-injured skin. In fact, in 1991, a Nobel Prize was awarded to two German scientists (Erwin Neher and Bert Sakmann, Nobel Assembly press release 1991), for their work in detecting subtle electrical currents in all types of cell membranes throughout the body .

Clinically, electrical stimulation has been used to heal wounds for years. In 1978, Becker showed the benefit of a continuous 0.9 volts direct microcurrent applied to an open orthopedic wound. Ferrier et al., (1986) observed osteoclasts migrating towards the anode when exposed to bioelectric current. This technology is currently being used to treat bone fractures and has FDA approval for its use to stimulate bone fracture non-unions.

It is well documented that endogenous electrical activity is present in mammalian skin. With skin injury, physiologic electrical activity helps cells migrate throughout the wound site. This electrical signal is essential to the cascade of reactions and processes required to initiate and sustain wound healing, especially cell transport to the injury site. Cells are transported along electrical currents lines which are generated in wounds through a process called galvanotaxsis. Keratinocytes, neutrophils, mast cells, and microbes migrate in the presence of low level microcurrents (Vanable, 1989). Utilizing the potential benefits of microcurrents in wounds, researchers have looked at the effects of applying close proximity electrically active wound dressings to a variety of wounds. Application of these devices to injured sites have been shown to augment wound healing (Wolcott et al., 1969 and Gault et al., 1976). Defined as the use of a capacitive coupled electrical current to transfer energy to a wound, the application of direct microcurrents to wounds resulted in enhanced healing. Anecdotally, in clinical settings, it was also observed to reduce pain and inflammation at the wound site.

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