Novel Antibiotic-Eluting Wound Dressings: *In-vitro* and *In-vivo* Study and Engineering Aspects in the Dressing's Design

Jonathan J. Elsner[1], Dana Egozi[2], Yehuda Ullman[2,3], Israela Berdicevsky[3] Adaya Shefy-Peleg[1], Meital Zilberman[1]

[1]Dept. of Biomedical Engineering, Tel-Aviv University, Tel-Aviv ISRAEL, [2]Dept of Plastic Surgery and Burn Unit, Rambam Medical Center, Haifa, ISRAEL, [3]Faculty of Medicine, Technion – Israel Institute of Technology, Haifa, ISRAEL

Statement of purpose: Despite advances in treatment regimens and the best efforts of nurses and doctors, approximately 70% of all people with severe burns die from related infections. Silver ion-eluting wound dressings are available to overcome this problem, but there are reports of deleterious effects of such dressings due to cellular toxicity that delays the healing process. Furthermore, dressing changes needed 1-2 times a day are uncomfortable for the patient and time consuming for the staff. A composite occlusive dressing material, based on a polyglyconate mesh, coated with a porous Poly(*DL*-lactic-co-glycolic acid) (PDLGA) matrix is described herewith. It is designed to protect the wound until it is no longer needed, after which it dissolves away by chemical degradation to non-toxic products. Avoiding constant wound cleaning and redressing should enable the body to better cope with healing and reduce patient pain and suffering.

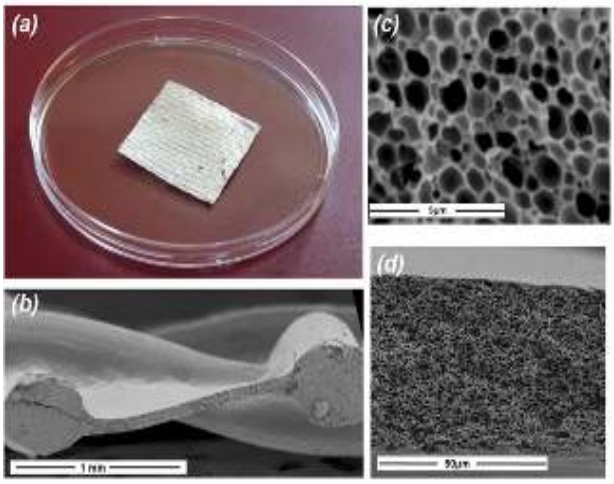

Figure 1 A biodegradable composite wound dressing structure composed of fibers surrounded by a continuous porous matrix (a). Cross-sectional SEM images demonstrate the basic unit structure (b) and the microstructure of the porous matrix (c, d).

Methods: Wound dressings were prepared by coating fibrous polyglyconate meshes with a porous polymer matrix, which was prepared using the freeze-drying of inverted emulsions technique [1,2]. Antibiotic (gentamicin/ ceftazidime) release from the dressings was tailored via microstructural and chemical modifications of the matrix during preparation. Microbiological (inhibition zone and time-kill) evaluations materials were conducted to elucidate the effect of the type of drug, its release rate and burst effect on bacterial inhibition. The cytotoxic effect of controlled release of antibiotics was also examined on fibroblast cultures. An *in vivo* evaluation of select dressing material was conducted in contaminated deep second degree burn wounds in guinea pigs (n=20). Wound regeneration was evaluated by examining contraction, epithelialization, and histology.

Results: The freeze-drying of inverted emulsions technique was found to be very useful in enabling to attain dressing materials with a wide range of burst effects (5-95%) and varying elution spans (5-50 days), based on predominantly on microstructuring of the matrix. Select compositions were found to produce a 99.99% decrease in the viable counts of very high initial inoculations of 10^7-10^8 CFU ml^{-1} of *Pseudomonas aeruginosa* and *Staphylococcus albus* after only 1 day, and a similar decrease in *Staphylococcus aureus* counts within 3 days. Bacterial inhibition zones around the dressing material were found to persist for 2 weeks, indicating a long-lasting antimicrobial effect. Despite severe toxicity to bacteria, the dressing material was found to have no toxic effect on cultured fibroblasts. *In vivo* evaluation of the dressing material in contaminated deep second degree burn wounds in guinea pigs demonstrated its ability to accelerate epithelialization by 40% compared to an unloaded format of the material and a conventional non-adherent dressing material. Wound contraction was reduced significantly, and a better quality scar tissue was formed. Faster epithelialization of the wound was measured in both fast and slow release strategies, but was significantly better when treated with a slow release rate.

Figure 2. Burn wounds contamination with *P.aeruginosa* and treated with a non-adherent dressing (Melolin®) remained open after 2 weeks (a), whereas wounds treated with the proposed material at fast and slow release rates of gentamicin (b, c respectively) demonstrate better epithelialization.

Conclusions: The composite dressing material exhibits promising results in terms of bacterial inhibition and safety. It does not require bandage changes and offers a potentially valuable and economic approach for treating the life-threatening complication of burn-related infections.

References: [1] Elsner J.J. Acta Biomater. 2009**;** 5: 2872-2883. [2] Elsner J.J. J Biomed Mater Res B. 2010; 93(2):425-35.