# New Thinking in Wound Healing: Reestablishing Microbiome Homeostasis to Restore Wound Healing with a Unique, 3D Nanofabricated Polymer Scaffold

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## INTRODUCTION

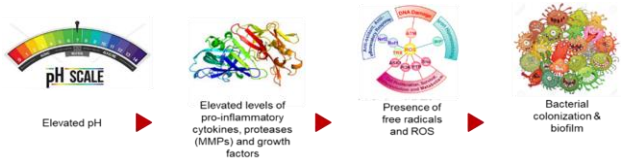
Non-healing wounds, burns and ulcers affect approximately 8 million Americans annually with a total cost of care to the health system of approximately $25B[1]. Alarmingly, chronic non-healing wounds such as, DFUs, VLUs, pressure injuries and ulcers of mixed etiology, are responsible for the greatest number of skin disease deaths (~30%) after skin cancer[1]. The statistics are staggering, and furthermore, as a result of the aging population and patients living with diabetes, the mortality rates associated with chronic non-healing wounds is now being considered by some, a silent epidemic[2].

Advancements in the science of wound healing, the study of the skin microbiome, and the desire to reestablish or maintain an acute-phase physiologic environment optimal for wound healing, has led to the development of a novel nanofabricated synthetic polymer technology comprised of naturally inherent structures known to encourage homeostasis and the body's natural wound healing process.

The commercialization of a novel 3D nanofabricated polymer scaffold, PHOENIX Wound Matrix, was designed to support and reestablish the body's natural wound healing process. This study is to evaluate the safety and efficacy of PHOENIX Wound Matrix for definitive wound closure.

## RETHINKING THE PROBLEM – AN ALTERED SKIN MICROBIOME FUELS CHRONIC ACTIVITY

Injured skin elicits an immediate reparative response, involving four phases: hemostasis, inflammation, proliferation and remodeling. However, normal cellular functions and interactions are dependent on a homeostatic, "healthy-state" microbiome. Loss of microbiome homeostasis, often results in healing dysfunction manifested by a sustained/stalled inflammatory phase.[1-5] In addition to modulating the innate immune response, the skin's flora acts as a mediator to control and encourage homeostasis.[4] Studies have shown the human microbiome varies spatially, therefore the skin microbiota varies from one site to another as a result of preferences for specific physiological characteristics such as pH, temperature, moisture and oxygen content.[3, 10]



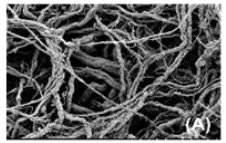

**Addressing pH and chronic activity**

It is known that pH plays a vital role in wound healing and acts as a mediatory to healthy cellular function. The pH of an acute phase wound supports the proper cellular function and balanced wound milieu that enables the body to naturally progress through the healing process to regenerate and repair tissue. In contrast to an acute wound, chronic wounds have an altered physiologic environment and tend to have high levels of pH, 7.15–8.9. Elevated pH breaks down cellular function and creates an alkaline wound environment, which fuels a host of endotoxic activity, including increased microbial loads, excessive proteolytic and protease-inhibitor activity and decreases tissue oxygenation. [11-17] This endotoxic activity disrupts the homeostatic microbiome and alters the body's natural response to wound healing making it an extremely complex process as there is not just one factor that needs to be addressed. [17-18].

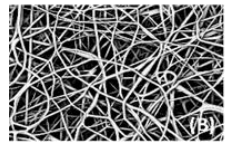
## NEW THINKING IN WOUND HEALING: PHOENIX WOUND MATRIX

Phoenix Wound Matrix is a novel, 3D nanofabricated synthetic polymer scaffold scientifically designed to inspire an acute-like, pro-healing wound environment, allowing the body's natural wound healing process to achieve definitive closure of complex acute wounds, chronic wounds and burns.
The 3D morphology of Phoenix mimics native hemodynamic ECM which supports cellular adhesion, infiltration and proliferation. Phoenix is comprised of two polymers that have been selected to support a low wound pH and through hydrolysis, naturally biodegrade into α-hydroxy acids and fatty acids known to facilitate angiogenesis and oxygenation to reestablish a balanced wound microbiome, tissue homeostasis and restore the body's natural wound healing process for tissue regeneration and repair.

In this case series, four patients were evaluated utilizing Phoenix Wound Matrix to determine its safety, clinical efficacy and outcomes on a variety of very challenging wounds.




Native Dermal ECM

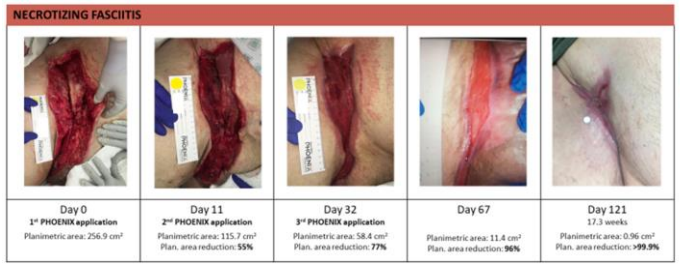



PHOENIX Wound Matrix

PHOENIX cellular adhesion, infiltration and proliferation

## CLINICAL OUTCOMES: Case Briefs

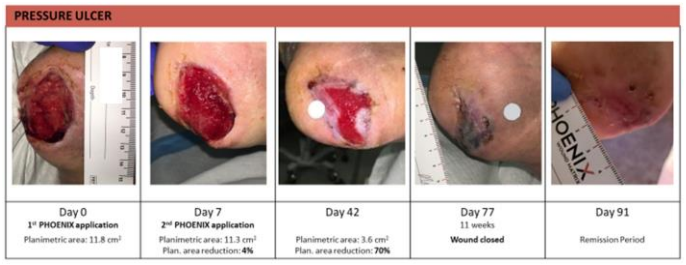
**NECROTIZING FASCIITIS**




**77%** reduction in wound area at 4 weeks

57-year-old male with type 2 diabetes and hypertension, presented 3-weeks after sustaining a fall to the sacral area. Resulting wound extended from upper right inguinal region, through perineum, to perianal area. Patient was diagnosed with necrotizing fasciitis, requiring extensive surgical debridement, antibiotics, and hyperbaric oxygen therapy (HBOT). Patient reported significant wound pain requiring pain medication for dressing changes. PHOENIX Wound Matrix was applied to anterior aspect of wound in conjunction with negative pressure wound therapy (NPWT). **By Day 11, a 55% decrease in wound size with healthy granulation tissue was observed.** Patient reported considerable decrease in pain, no longer required pain medication. By **Day 32 anterior wound decreased by 77%. By Day 67, 96% reduction in planimetric area was achieved.** Wound closure was achieved on Day 125 after **3 PHOENIX applications** combined with wound care best practices, including HBO and NPWT.

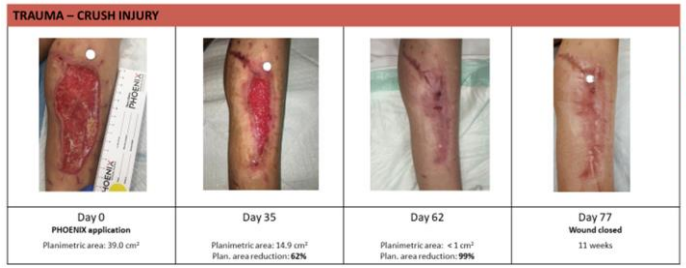
**PRESSURE ULCER**




**70%** reduction in wound area at 6 weeks

90-year old male with **paraplegia** presented with right heel **pressure ulcer of over 4 months duration**. Additionally, at presentation, a **2.2 cm tunnel** was observed superomedially. Despite receiving best practice standard of care plus other advanced modalities, patient developed osteomyelitis and required surgical debridement. Following surgical debridement, the 1st PHOENIX Wound Matrix was applied on Day 0. Robust granulation tissue was noted within days; second PHOENIX was applied on Day 7, and accelerated progress continued. On Day 42, 70% decrease in planimetric area was observed. **Full wound closure was achieved on Day 77 after 2 applications of PHOENIX Wound Matrix.**

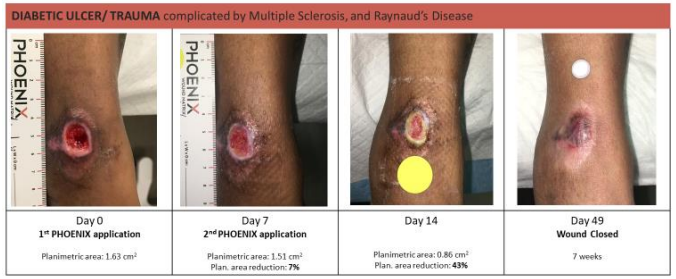
**TRAUMA – CRUSH INJURY**




**62%** reduction in wound area at 4.5 weeks

10-year-old female sustained a traumatic crush injury to her left anteromedial leg. Patient required extensive surgical debridement of a failed flap repair and received HBOT and NPWT for 14 days. PHOENIX Wound Matrix was introduced into treatment strategy to restore wound healing combined with HBOT and NPWT. **A 62% reduction in wound area was achieved in 4.5 weeks.** Patient made steady, remarkable progress **achieving wound closure on Day 77 with 1 PHOENIX application.**

**DIABETIC ULCER/ TRAUMA** complicated by Multiple Sclerosis, and Raynaud's Disease




**43%** reduction in wound area at 2 weeks

40-year-old female with history of type 1 diabetes, multiple sclerosis, and Raynaud's disease, presented to the wound care clinic status post a fall 4 weeks earlier. Following thorough debridement, PHOENIX was applied. Wound depth was visibly reduced within 1 week of treatment. **The planimetric area decreased by 43% after 2 weeks of treatment and 2 applications of PHOENIX.** The wound closed following 49 days of treatment.

**References: 1.** Lim, H. W., S.A.B Collins, J.S. Resneck, Jr, et al. 2017. The burden of skin disease in the United States. J. Am. Acad. Dermatol. 76: 958-972.e2.; **2.** Driver, V.R., R.J. Snyder, T. Conner-Kerr & T. Thomas. 2014. AAWC Fact Sheet 1: CHRONIC WOUNDS The most important health problem you've never heard about. AAWC. Accessed January 24, 2018. https://s3.amazonaws.com/aawc-new/memberclicks/Fact-sheet-1-final_May-2014.pdf; **3.** Grice, E.A. and J.A. Segre, The skin microbiome. Nat Rev Microbiol, 2011. 9(4): p. 244-53.; **4.** Capone, K.A., et al., Diversity of the human skin microbiome early in life. J Invest Dermatol, 2011. 131(10): p. 2026-32.; **5.** Weyrich, L.S., et al., The skin microbiome: Associations between altered microbial communities and disease. Australas J Dermatol, 2015. 56(4): p. 268-74.; **6.** Kalan, L. and E.A. Grice, Fungi in the Wound Microbiome. Adv Wound Care (New Rochelle), 2018. 7(7): p. 247-255.; **7.** Kalan, L., et al., Redefining the Chronic-Wound Microbiome: Fungal Communities Are Prevalent, Dynamic, and Associated with Delayed Healing. MBio, 2016. 7(5).; **8.** Cho, I. and M.J. Blaser, The human microbiome: at the interface of health and disease. Nat Rev Genet, 2012. 13(4): p. 260-70.; **9.** Jones, E.M., C.A. Cochrane, and S.L. Percival, The Effect of pH on the Extracellular Matrix and Biofilms. Adv Wound Care (New Rochelle), 2015. 4(7): p. 431-439.; **10.** Schneider, L.A., et al., Influence of pH on wound-healing: a new perspective for wound-therapy? Arch Dermatol Res, 2007. 298(9): p. 413-20.; **11.** Gethin, G., The significance of surface pH in chronic wounds. Wounds UK, 2007. 3.; **12.** B, G., et al., Proteases and pH in chronic wounds. Journal of Wound Care, 2005. 14(2): p. 59-61.; **13.** TK, H. and B. S, Theoretical and Practical Aspects of Oxygen in Wound Healing, in The Wound Management Manual, L. B, Editor. 2005, McGraw-Hill: New York. p. 44-54.; **14.** Leveen, H.H., et al., Chemical acidification of wounds. An adjuvant to healing and the unfavorable action of alkalinity and ammonia. Annals of surgery, 1973. 178(6): p. 745-753.; **15.** Das, A., et al., Monocyte and macrophage plasticity in tissue repair and regeneration. Am J Pathol, 2015. 185(10): p. 2596-606.; **16.** McCarty, S.M. and S.L. Percival, Proteases and Delayed Wound Healing. Adv Wound Care (New Rochelle), 2013. 2(8): p. 438-447.; **17.** NJ, T., et al., Analysis of the acute and chronic wound environments: the role of proteases and their inhibitors. Wound Repair Regen., 1999. 7(6): p. 442-52.; 18. Zheng, X.F., et al., Lipopolysaccharide-induced M2 to M1 macrophage transformation for IL-12p70 production is blocked by Candida albicans mediated up-regulation of EBI3 expression. PLoS One, 2013. 8(5): p. e63967.