EscharEx®
Mechanism of Action

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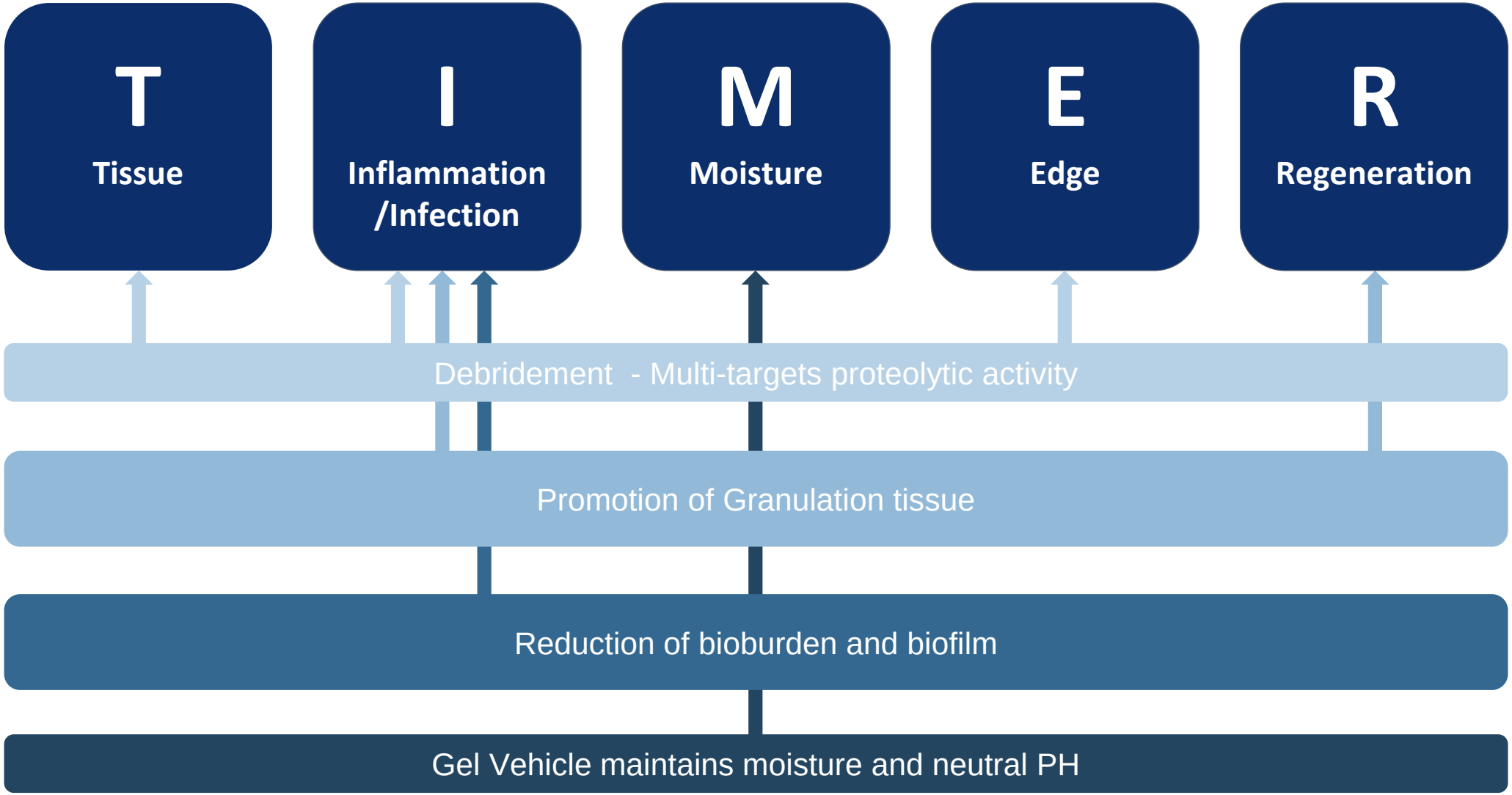
BBD Affects All Components of the TIMER Model[1]



1. Snyder et al. *Wounds 2024*

Multi-Targeted Proteolytic Activity

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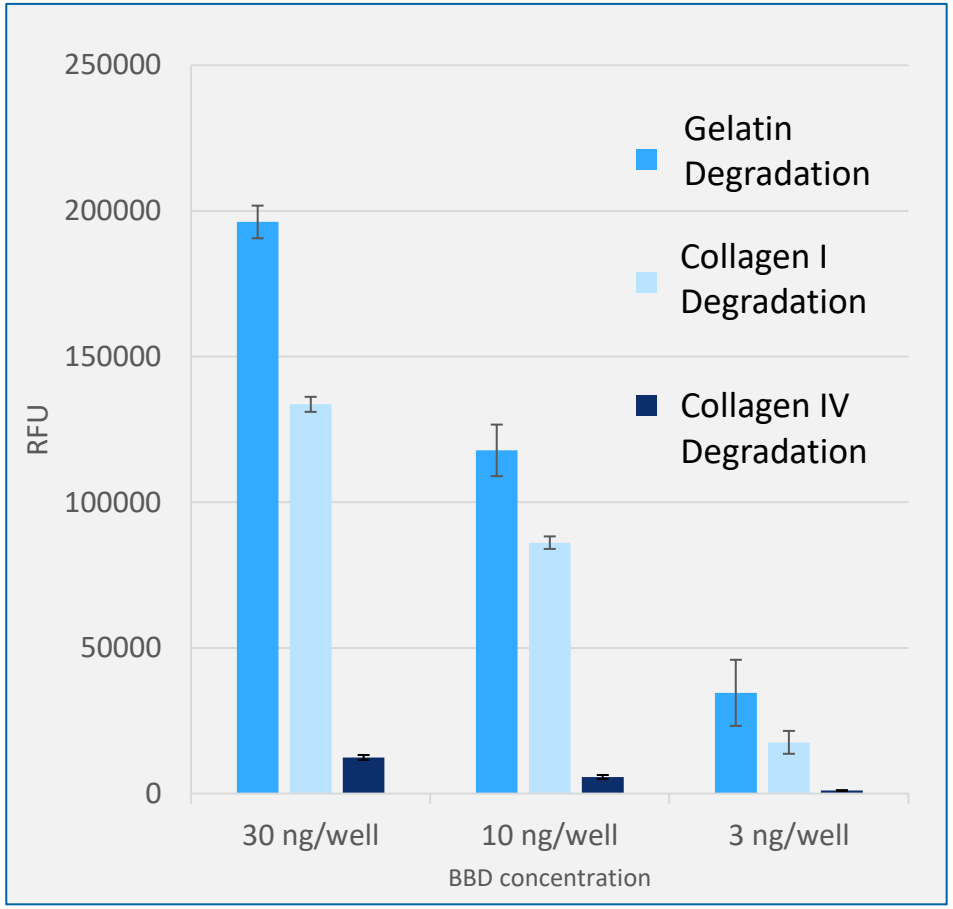
BBD has Higher Affinity Towards Denatured Collagen

- Eschar/non-viable tissue consists primarily of gelatin, a denatured form of collagen
- We tested the degradation rates[1] of:
  - Gelatin (abundant in necrotic tissue)
  - Collagen type I (abundant in necrotic tissue and skin)
  - Collagen type IV (abundant in the basement membrane)

EscharEx demonstrated higher affinity towards denatured collagen than towards the native forms of collagen

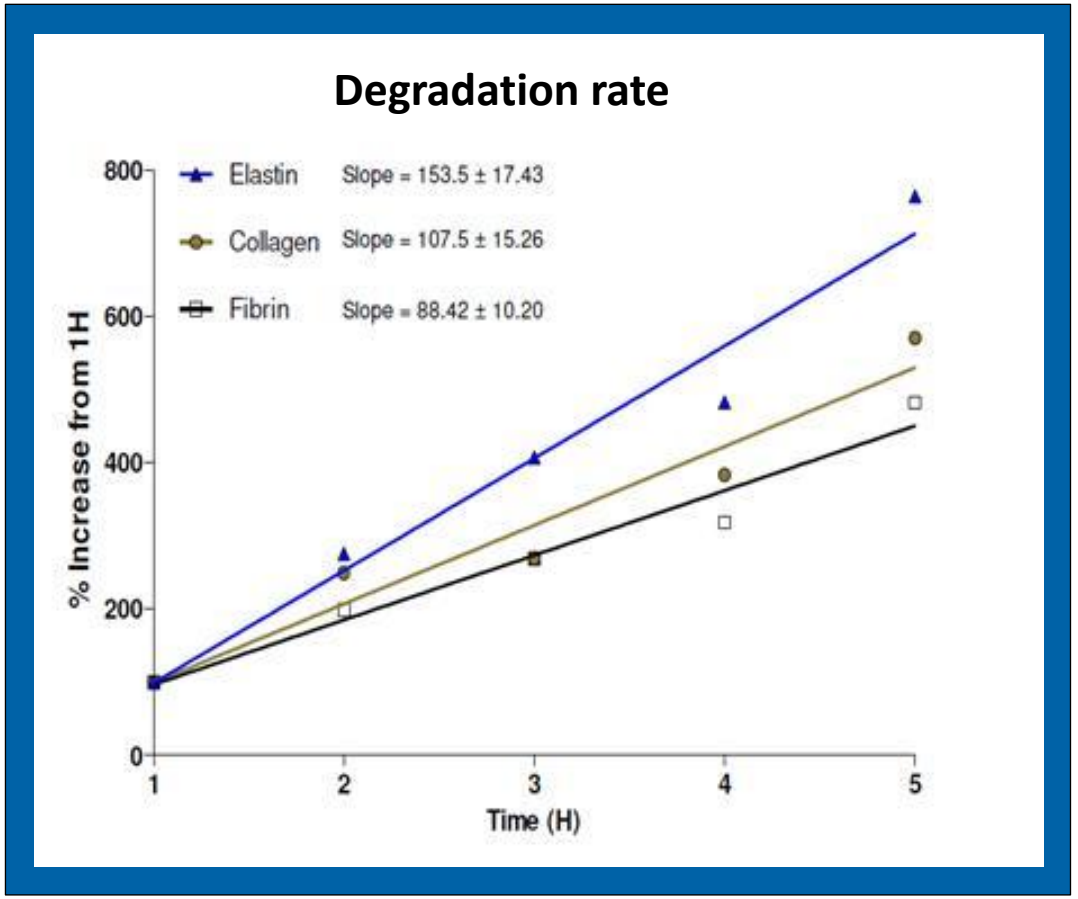


BBD activity was evaluated using fluorescently labeled native and denatured collagen

1. Data on file

BBD Degrades Over-Secreted ECM Proteins

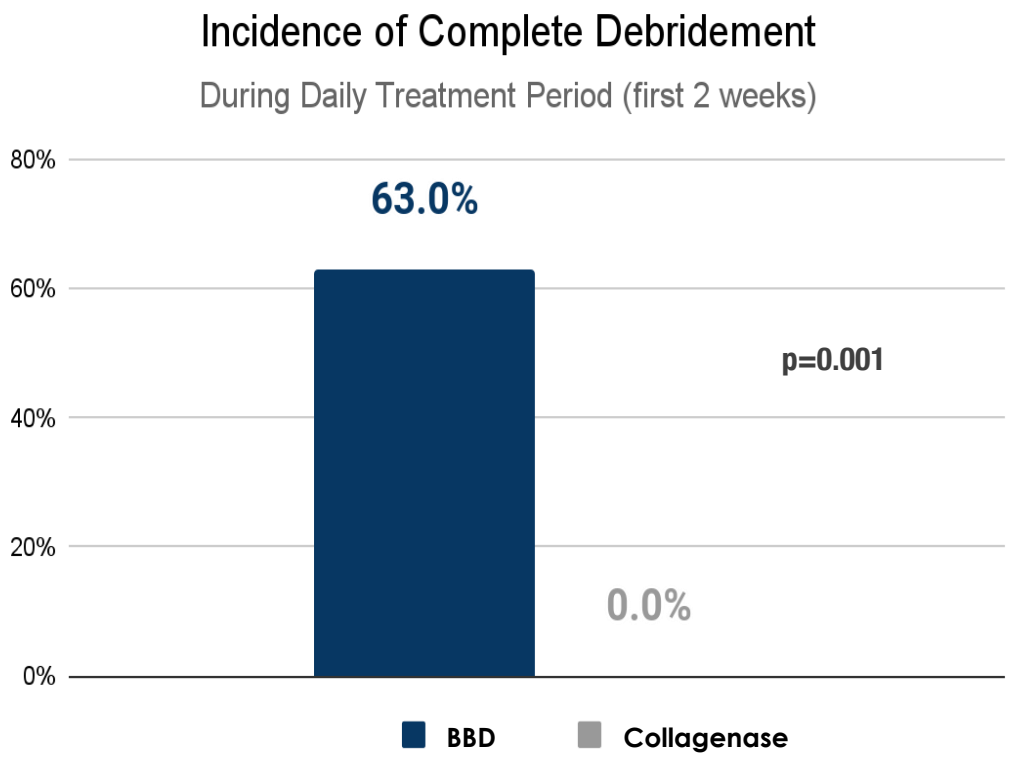
- ECM proteins (e.g. fibrin, collagen, elastin) are over-secreted in chronic wounds, and **prevent the progression to normal healing**
- BBD enzymes degrade over-secreted ECM proteins[1] and facilitate the removal of various denatured proteins from the wound bed

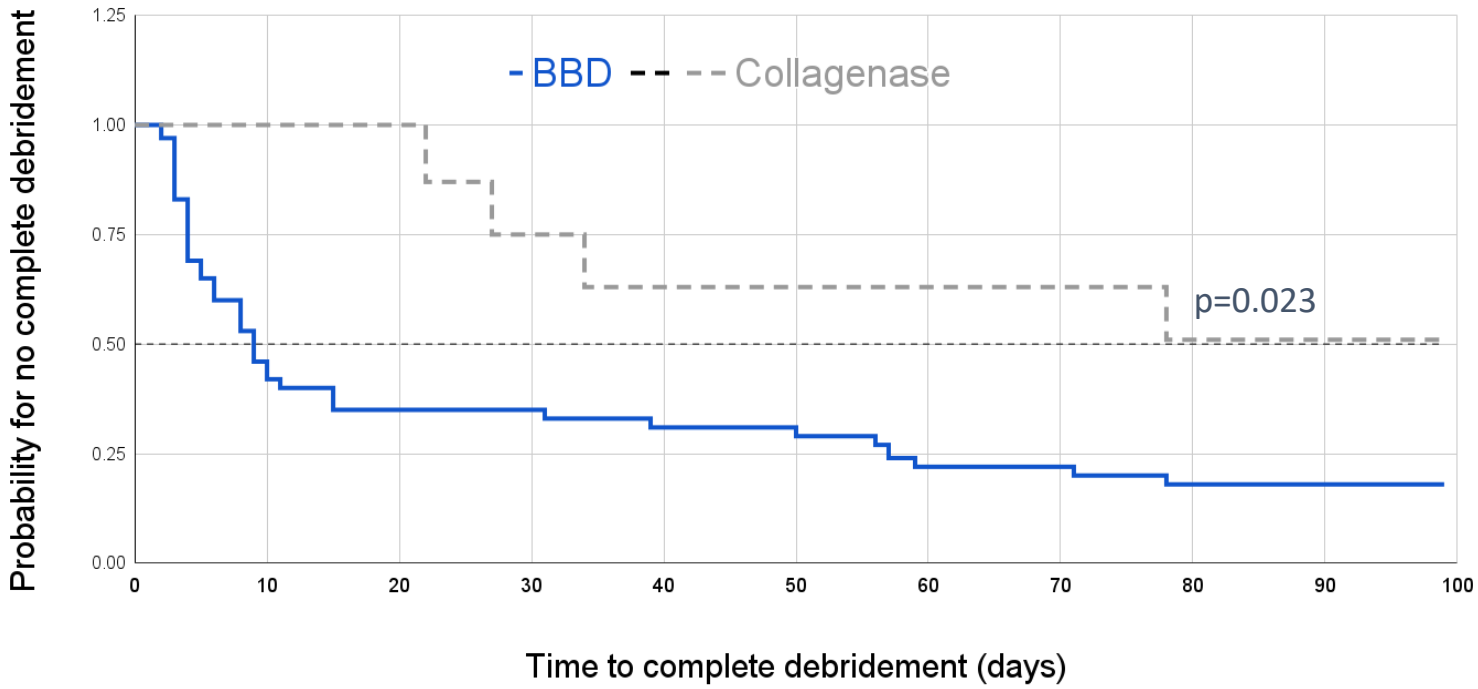


In vitro degradation of fluorescently labeled proteins by BBD, using Franz cells

1. Data on file

Subgroup Analysis from a Phase 2 RCT in VLU Patients [1]





Estimated median time to achieve complete debridement	
BBD	**Collagenase**
9 days (95% CI=5-15 days)	**not achieved** (95% CI=22-Not Applicable)

p=0.023

1. **Dove et al.** *Wounds* 2025 - In Press

Selective Removal of Denatured Collagen (In Deep Burns)

NexoBrid® indicated for eschar removal in deep thermal burns

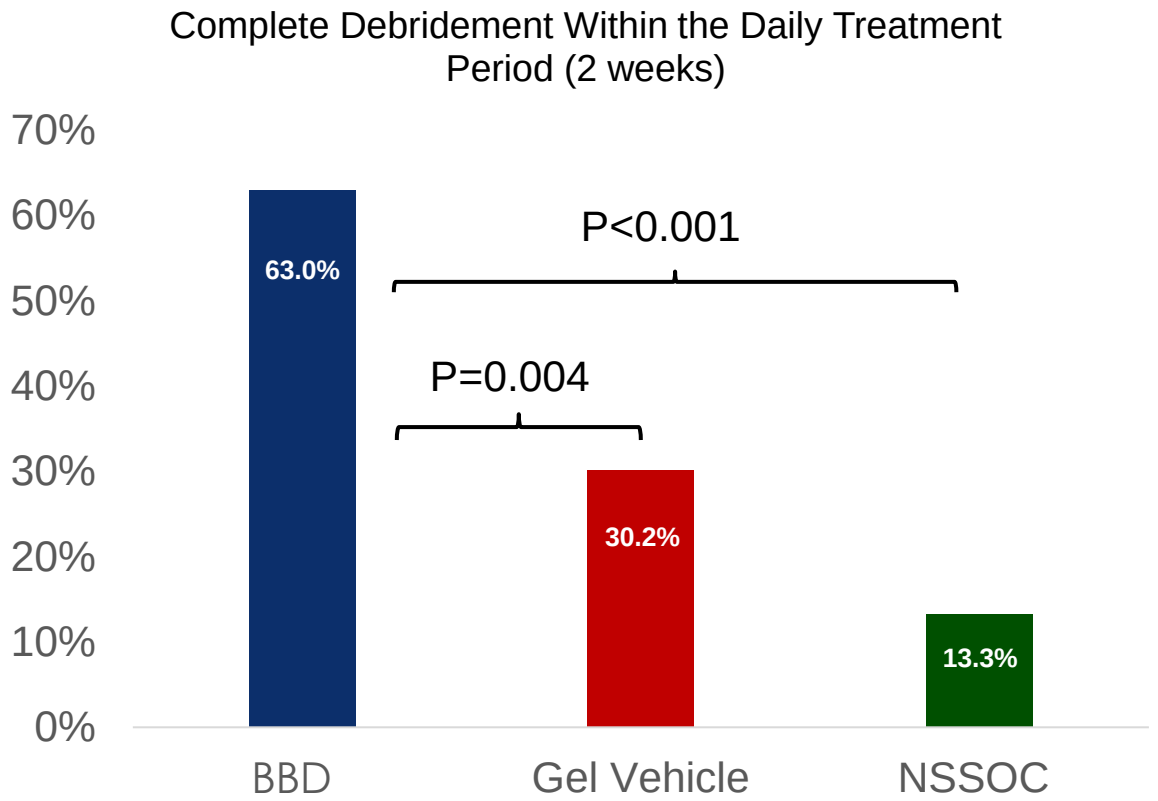
Approved in - US, Japan, India and Europe

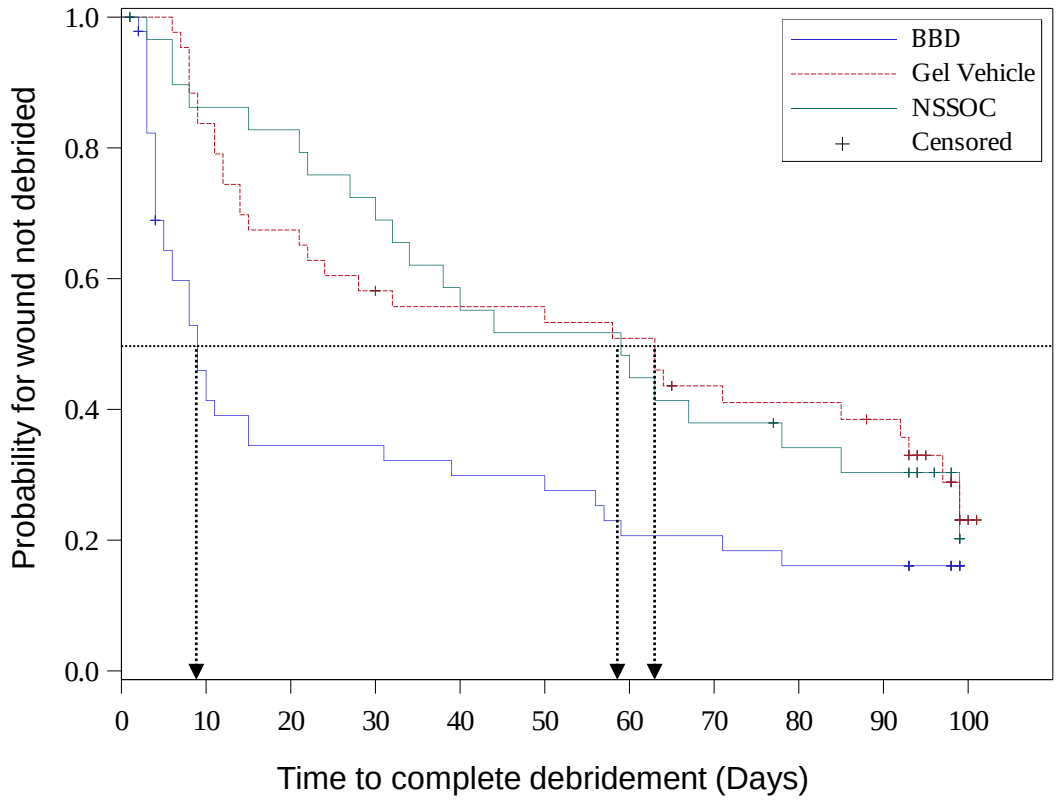
EscharEx - Enzymatic Debridement within Days

VLU
Venous Leg Ulcers
(Complete Debridement – 3 days)

DFU
Diabetic Foot Ulcers
(Complete Debridement – 4 days)

EscharEx - Fast and Effective Debridement





Significantly higher incidence of complete debridement vs. Gel Vehicle (primary end point) and vs. NSSOC

Median time to complete debridement: BBD: 9 days, NSSOC: 59 days, P=0.016

Promotion of Granulation Tissue

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Importance of Granulation Tissue on Wound Bed Preparation

Literature Review[1,2,3,4]

Key aspects of granulation tissue

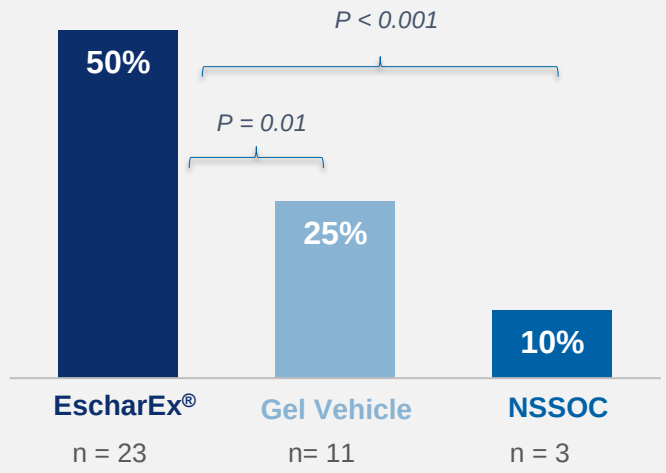
- *Angiogenesis*
- *Collagen deposition in the wound bed*
- *Fibroblasts proliferation and migration*
- *Wound contraction*
- *Protects against infection*
- *Promotes epithelial cells to migration*
- *Reduces inflammation*

1. Gurtner *Nature 2008;* **2. Martin** *British Journal of Dermatology 2015;* **3. Darby** *Clinical, Cosmetic and Investigational Dermatology 2014;* **4. Diegelmann** *Frontiers in Bioscience 2004*

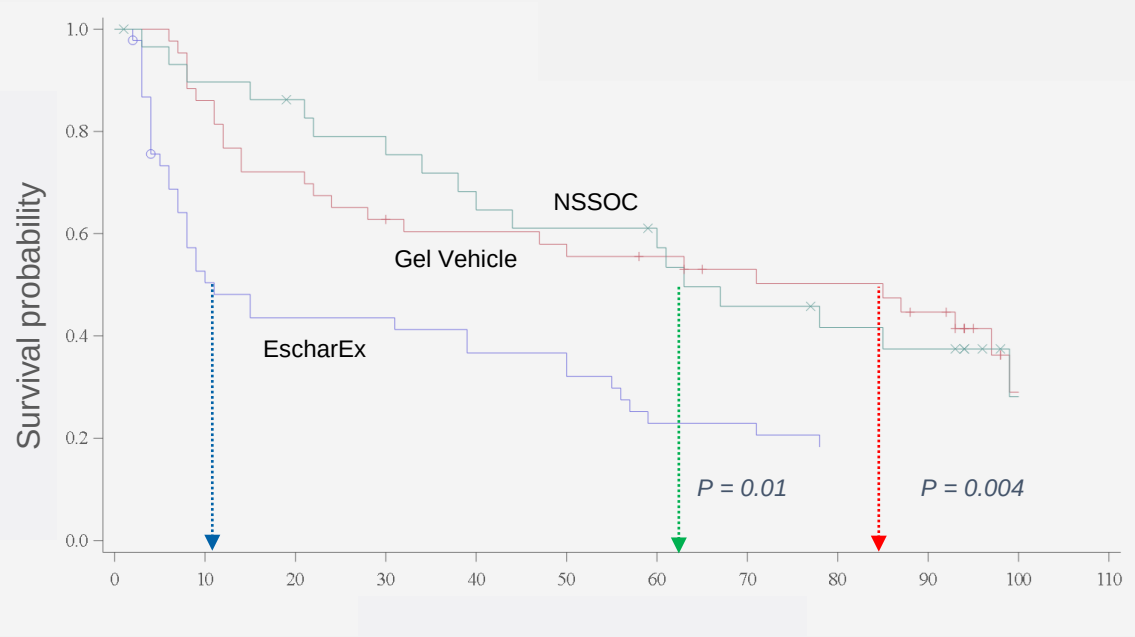
EscharEx – Fast and Effective Wound Bed Preparation

Phase II Data[1]

Incidence of WBP/ Complete Granulation in 2 weeks



Time to WBP/ Complete Granulation



Estimated Median time to WBP
EscharEx® 11 days vs. **Gel Vehicle** 85 days

1. **Shoham et al**. *eClinicalMedicine (Lancet group)* 2024

Bromelain Effect on Granulation

Literature Review[1]

Effect on growth factors, perfusion, and inflammatory mediators

- *TGF-β ↑ ñ inducing the formation and granulation tissue and differentiation of myofibroblasts*
- *VEGF ↑ - promote vascularization*
- *IL-6 ↑ - Regulation of myofibroblasts*

1. **Snyder et al.** *Wounds 2024*

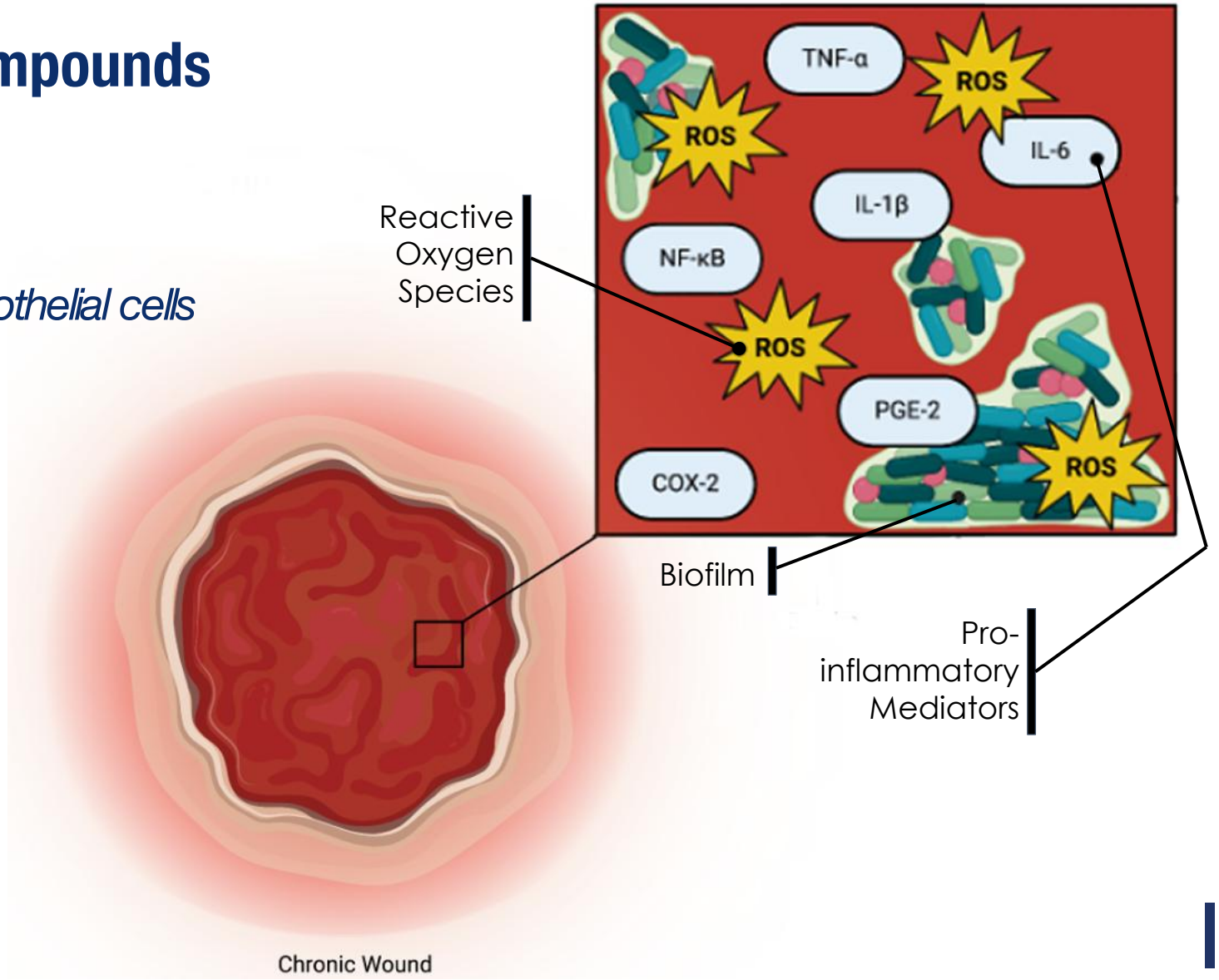
Anti-inflammatory Effects

MediWound

Bromelain Anti-inflammatory Effects

Pro-inflammatory Wound Compounds

- *Reduces pro-inflammatory cytokines:*
  - IL-1β, IL-6, TNF-α, PGE-2, NF-κB
- *Release of nitric oxide (NO) from endothelial cells*



Reduction of Bioburden and Biofilm Disruption

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Bromelain is Highly Effective in Degradation of Biofilm

- Watters et.al established a Staphylococcus aureus **biofilm model** that mimicked wound like conditions
- Antibiofilm activity of four enzyme compounds reviewed
- **Bromelain reduced biofilm mass by 98%**
- Scanning electron microscopy confirmed detachment of the biofilm EPS and bacteria from growth surfaces
- Overall, results indicated that enzymes such as **bromelain** may be an effective means of eradicating biofilms and a promising strategy to improve treatment of multidrug-resistant bacterial infections

Infection and Drug Resistance

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ORIGINAL RESEARCH

Enzymatic degradation of in vitro *Staphylococcus aureus* biofilms supplemented with human plasma

This article was published in the following Dove Press journal:
Infection and Drug Resistance
27 April 2016
Number of times this article has been viewed

Chase M Watters[1,2]
Tarea Burton[1]
Dickson K Kirui[1]
Nancy J Millenbaugh[1]

[1]Maxillofacial Injury and Disease Department, Naval Medical Research Unit San Antonio, Joint Base San Antonio-Fort Sam Houston, TX, USA; [2]Wound Infections Department, Naval Medical Research Center, Silver Spring, MD, USA

Abstract: Enzymatic debridement is a therapeutic strategy used clinically to remove necrotic tissue from wounds. Some of the enzymes utilized for debridement have been tested against bacterial pathogens, but the effectiveness of these agents in dispersing clinically relevant biofilms has not been fully characterized. Here, we developed an in vitro *Staphylococcus aureus* biofilm model that mimics wound-like conditions and employed this model to investigate the antibiofilm activity of four enzymatic compounds. Human plasma at concentrations of 0%–50% was supplemented into growth media and used to evaluate biofilm biomass accumulation over 24 hours and 48 hours in one methicillin-sensitive and five methicillin-resistant strains of *S. aureus*. Supplementation of media with 10% human plasma resulted in the most robust biofilms in all six strains. The enzymes α-amylase, bromelain, lysostaphin, and papain were then tested against *S. aureus* biofilms cultured in 10% human plasma. Quantification of biofilms after 2 hours and 24 hours of treatment using the crystal violet assay revealed that lysostaphin decreased biomass by up to 76%, whereas α-amylase, bromelain, and papain reduced biomass by up to 97%, 98%, and 98%, respectively. Scanning electron microscopy confirmed that the dispersal agents detached the biofilm exopolysaccharide matrix and bacteria from the growth surface. Lysostaphin caused less visible dispersal of the biofilms, but unlike the other enzymes, induced morphological changes indicative of bacterial cell damage. Overall, our results indicate that use of enzymes may be an effective means of eradicating biofilms and a promising strategy to improve treatment of multidrug-resistant bacterial infections.

Keywords: MRSA, α-amylase, bromelain, lysostaphin, papain

Phase II Trial: EscharEx Reduced Bioburden and Biofilm

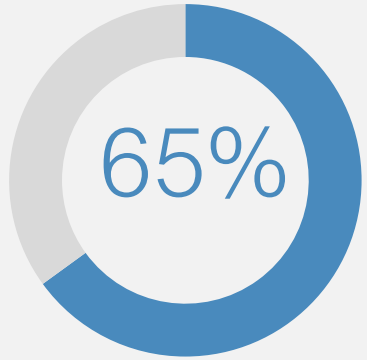
WOUNDS

ORIGINAL RESEARCH

An Open-Label, Proof-of-Concept Study Assessing the Effects of Bromelain-Based Enzymatic Debridement on Biofilm and Microbial Loads in Patients With Venous Leg Ulcers and Diabetic Foot Ulcers

Robert J. Snyder, Adam J. Singer, Cyaandi R. Dove, Stephen Heisler, Howard Petusevsky, Garth James, Elinor deLancey Pulcini, Aya Ben Yaakov, Lior Rosenberg, Edward Grant, Yaron Shoham

Keywords
Bacteria
Biofilm
Bromelain



Bioburden reduction by end of treatment

Biofilm reduced substantially for all patients positive for biofilm at baseline

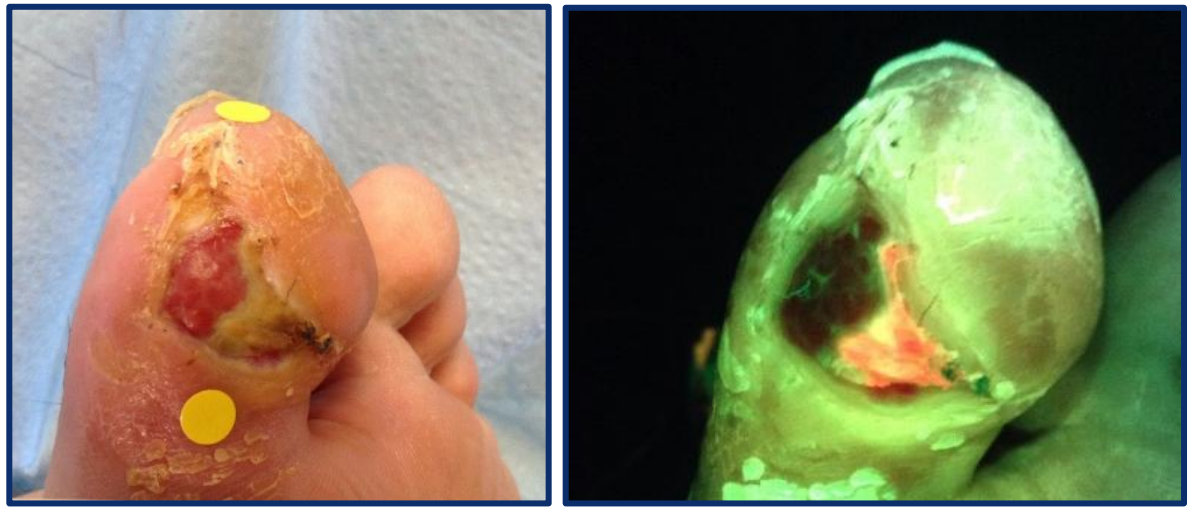
EscharEx – Reduced Bacterial Load

S 104-004

Pre-treatment

Red fluorescence area:

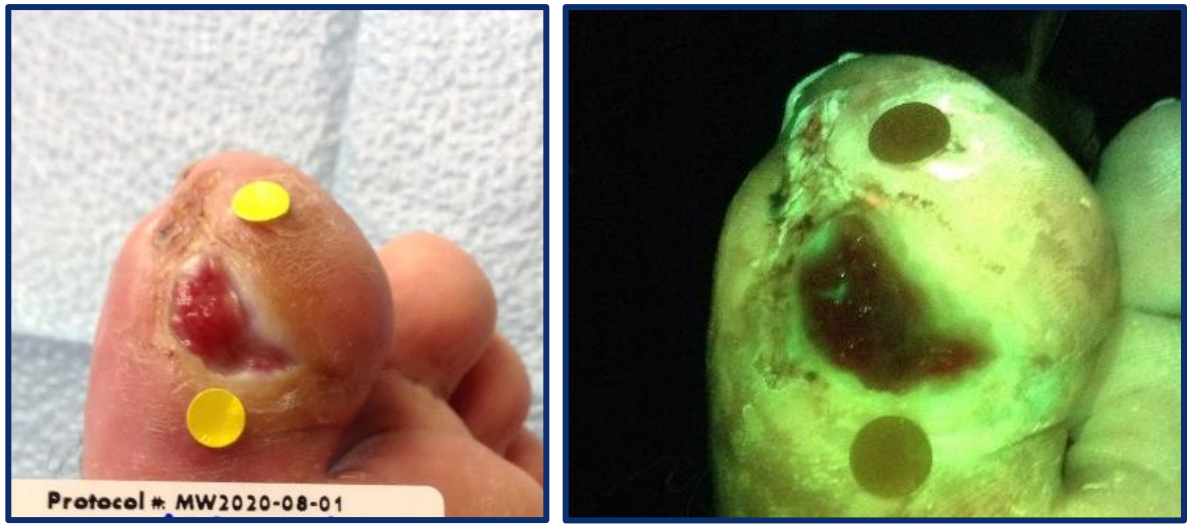
0.84 cm^2



Post treatment

Red fluorescence area:

0.2 cm^2



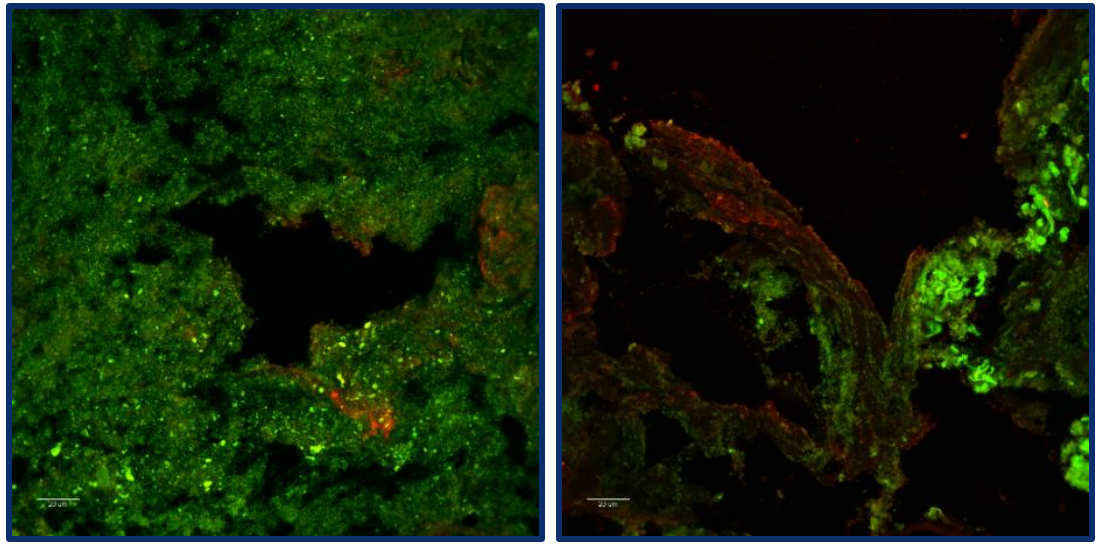
EscharEx Reduced Biofilm

S 101-001

Pre-treatment

Biofilm score: 5

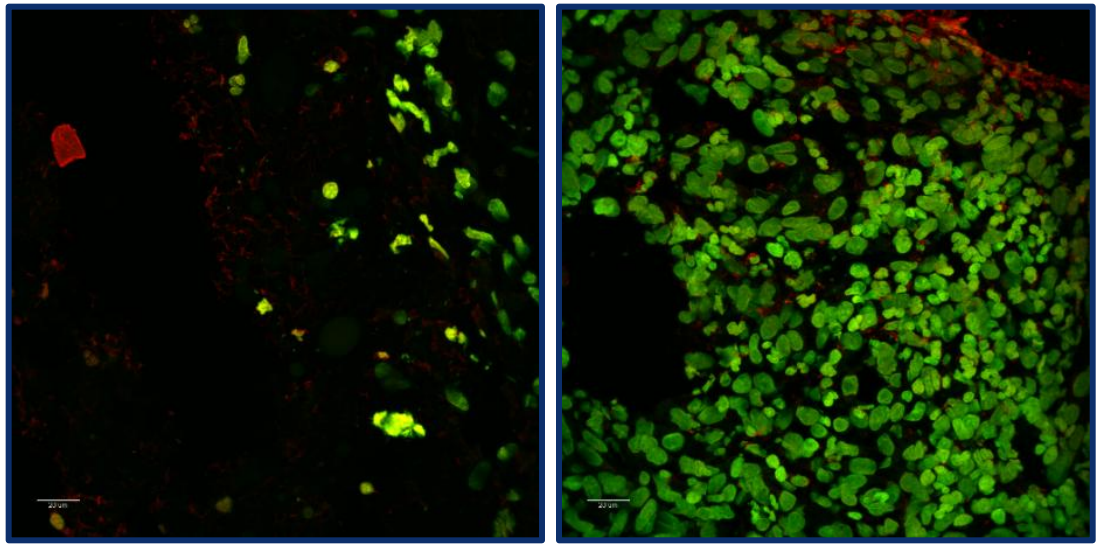
(Thick continuous film of microorganisms)



Post treatment

Biofilm score: 1

(Single individual microorganisms)



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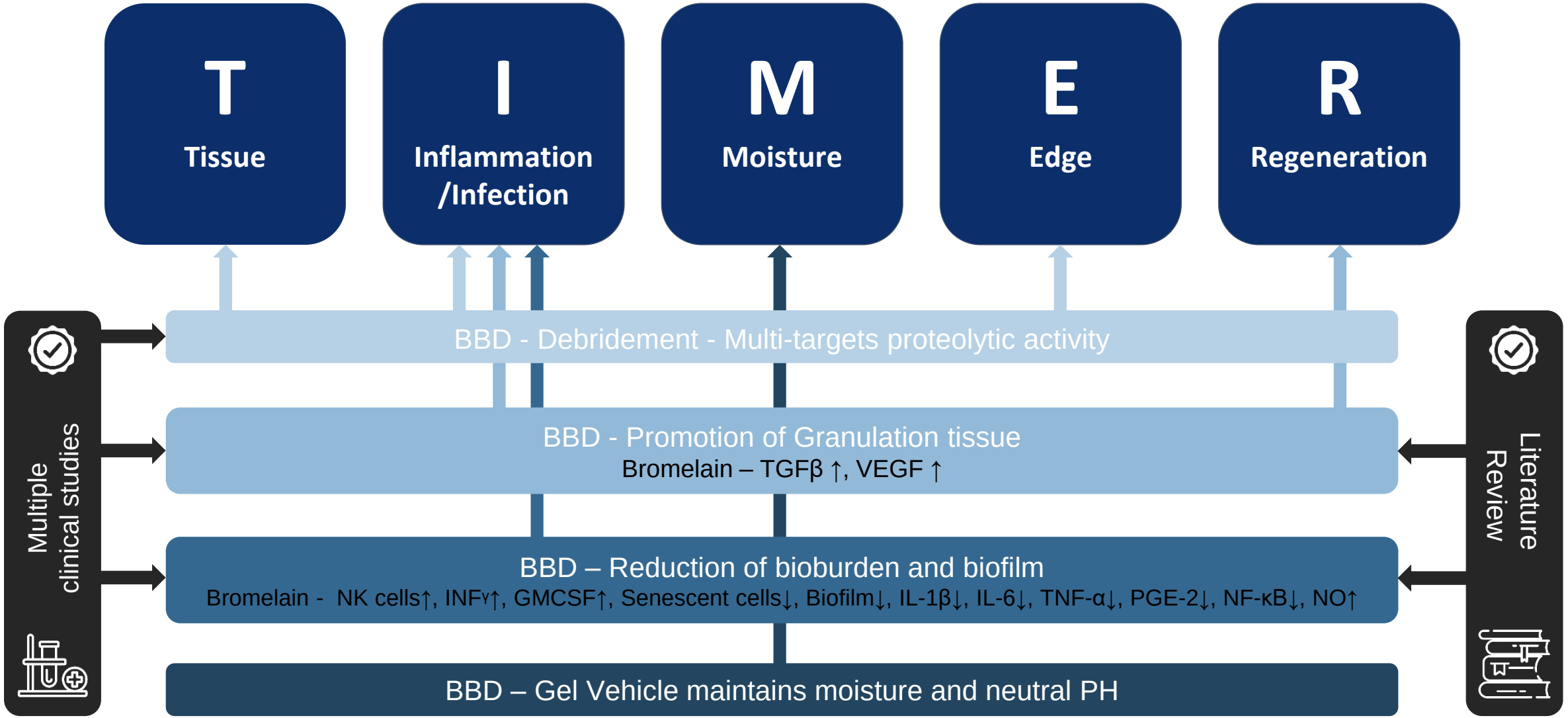

1. Snyder et al. *Wounds 2024*

Thank You!!