

Understanding and Managing MMP's in Wound Bed

Brock Liden DPM, ABPM, FAPWCA

Learning Objectives

- Review the four sequential phases of normal wound healing and recognize the **BENEFICIAL** effects of **CONTROLLED INFLAMMATION** and **PROTEASE ACTIVITIES**
- Understand the link between **CHRONIC INFLAMMATION** caused by **PLANKTONIC** and **BIOFILM BACTERIA** and **ELEVATED PROTEASE ACTIVITIES** that **DESTROY** proteins that are essential to healing (extracellular matrix, growth factors, receptors)
- Understand the **VARIATION** of proteases and their **IMPACT** on wound healing
- Discuss current approaches to **MANAGEMENT AND REMOVAL** of proteases from the wound bed

Four Phases of Wound Healing

Injury

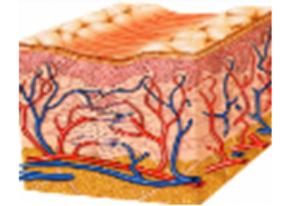
Closure

1-3 days

3 - 20 days

1 – 6 weeks

6 weeks to 2 yrs



- Vasoconstriction
- Platelet aggregation
- Blood clotting

Hemostasis

Inflammation

- Leukocyte migration
- Neutrophils
- Macrophages
- Release of cytokines & growth factors

- Neovascularization
- Fibroblast proliferation
- Secretion of collagen
- Keratinocytes migration
- Granulation tissue

Proliferative

Remodeling

- Fibroblast secretion of collagen and matrix proteins
- Wound contraction and remodeling

Four Phases of Wound Healing

Injury

1-3 days

3- 20 days

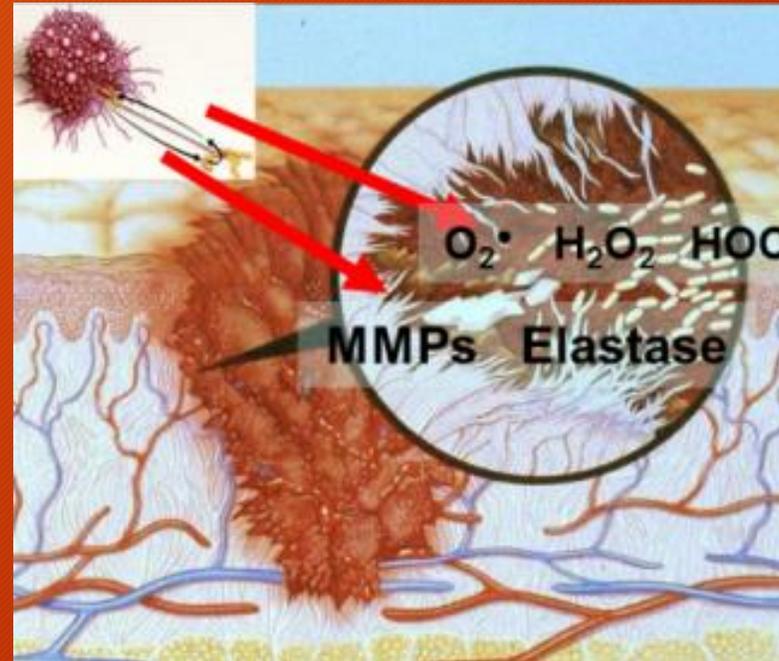
1 – 6 weeks

Closure

6 weeks to 2 yrs

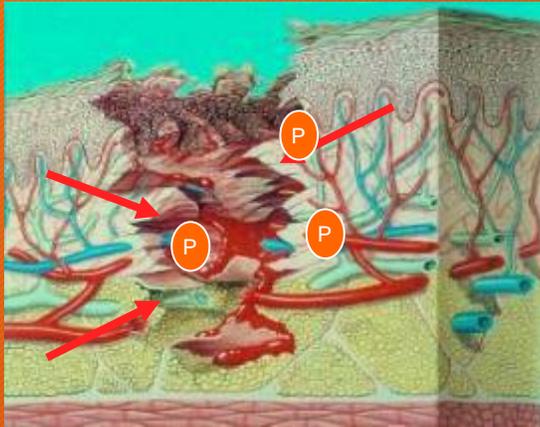
Inflammation

- Leukocyte migration
- Neutrophils
- Macrophages
- Release of growth factors

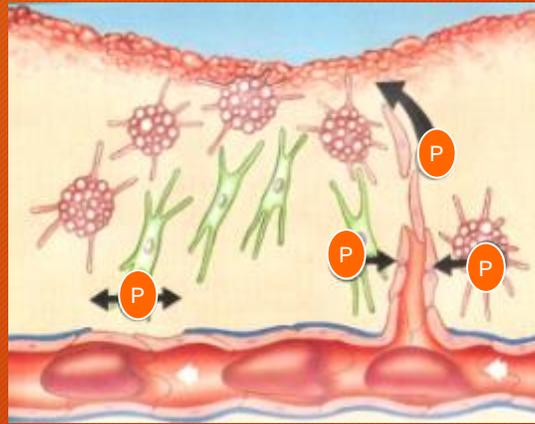


Controlled inflammation is beneficial

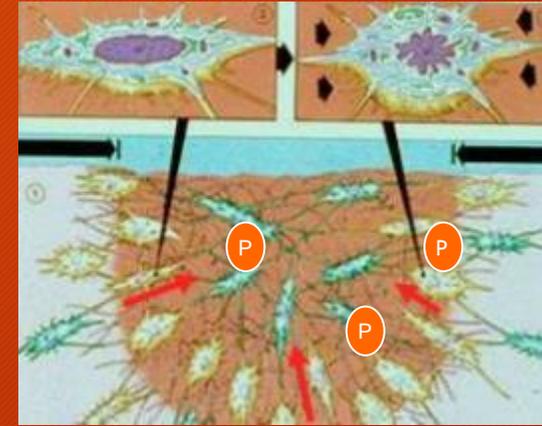
Matrix Metalloproteinases - MMPs Necessary for Wound Healing



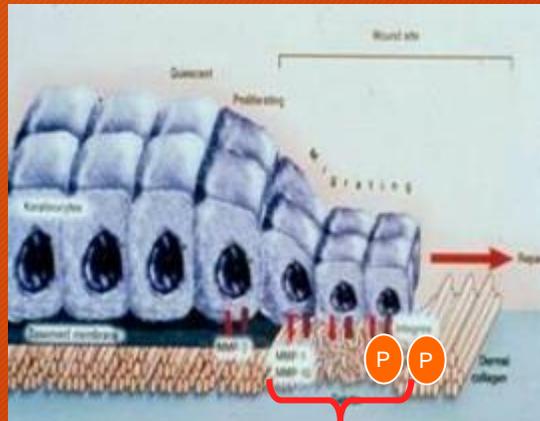
Debridement



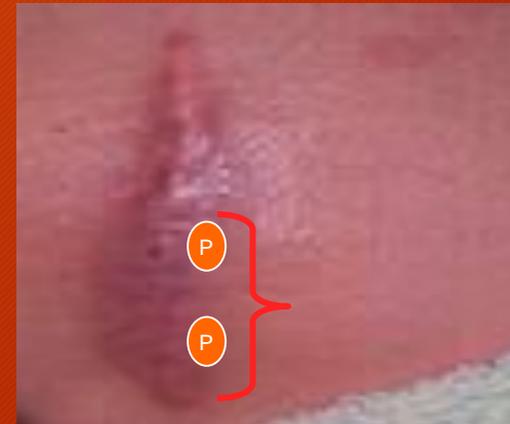
Angiogenesis



Contraction



Epithelial Migration

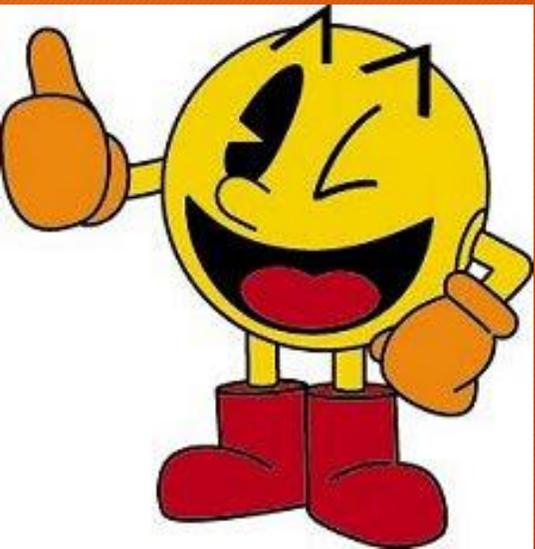


Remodeling

MMPs in Normal Wound Healing

MMPs are essential for normal wound healing, **BUT** must be:

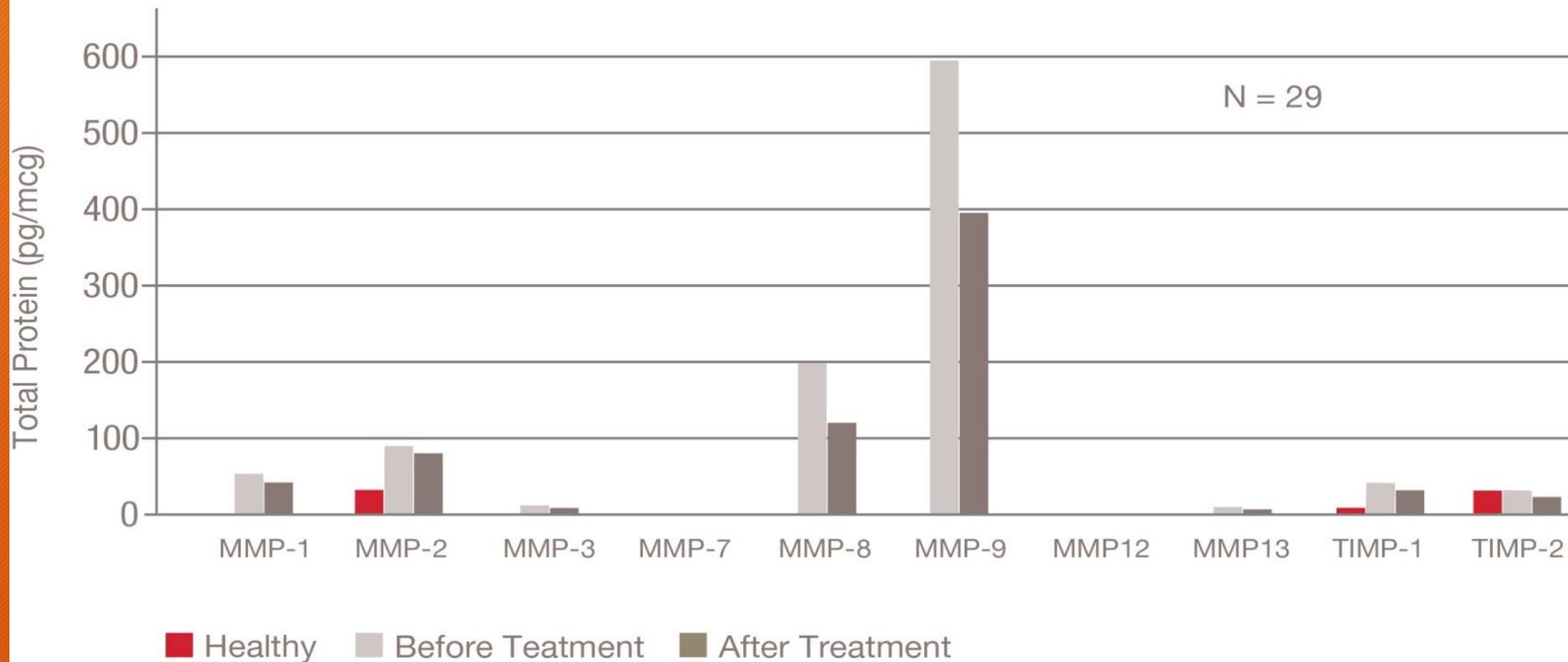
- At the right places
- At the right times
- At the right amounts

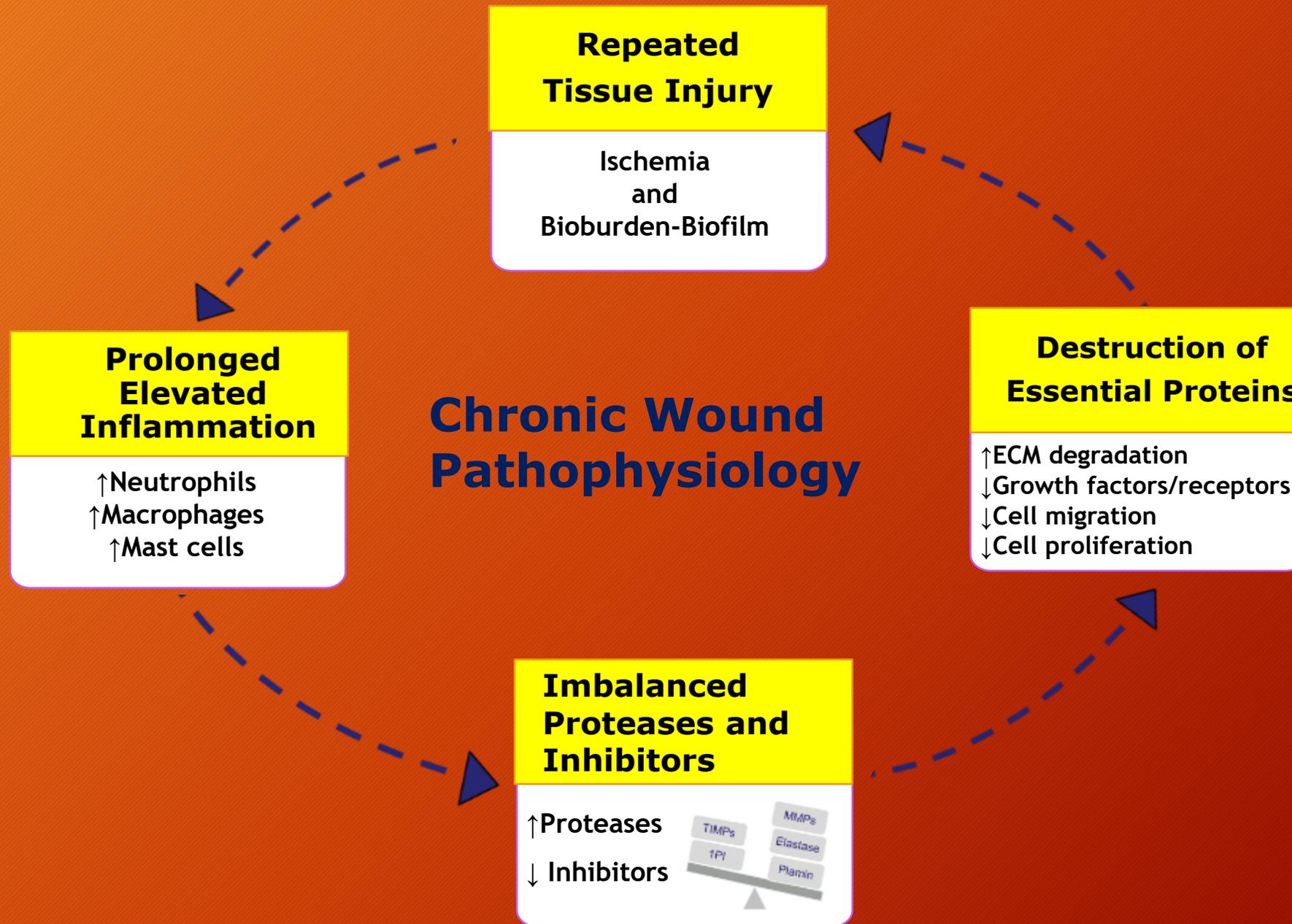


Venous Leg Ulcers are Inflammatory

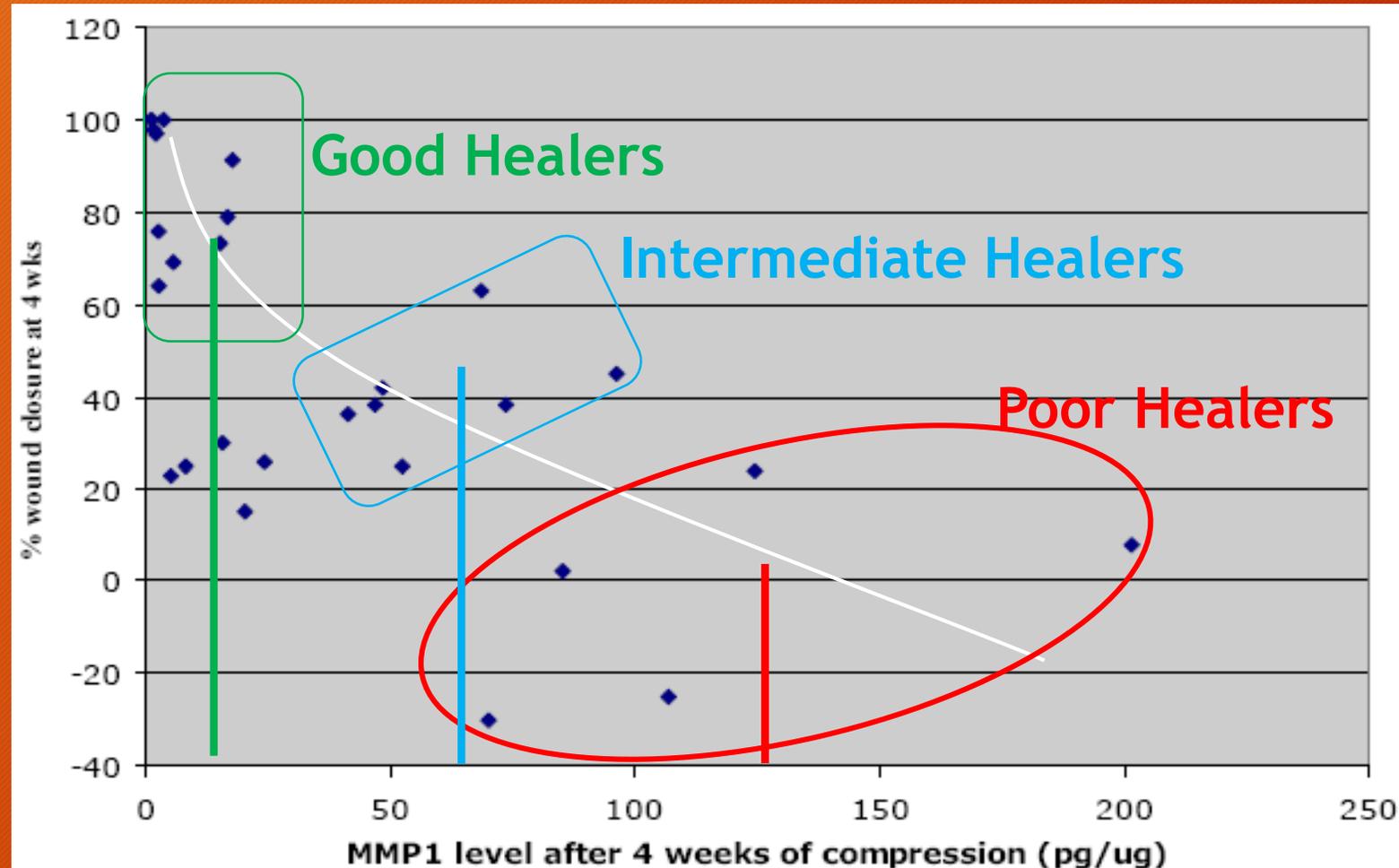
Relative MMP Levels in Healthy Tissue and Leg Ulcer Tissue before and after Compression Therapy

Relative MMP Levels in Healthy and Ulcer Tissue before and after Compression Therapy

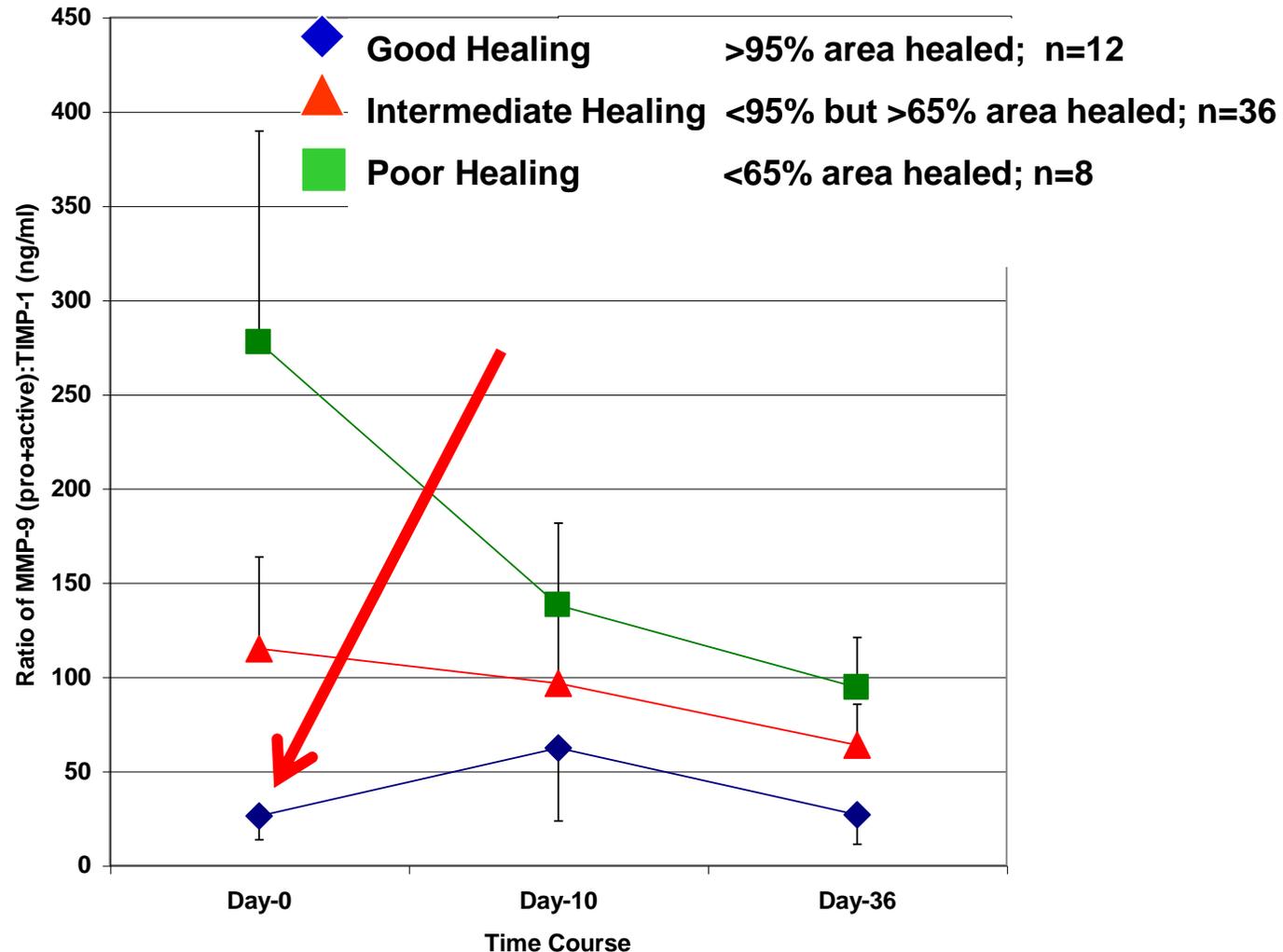




Elevated MMP-1 in Venous Ulcers

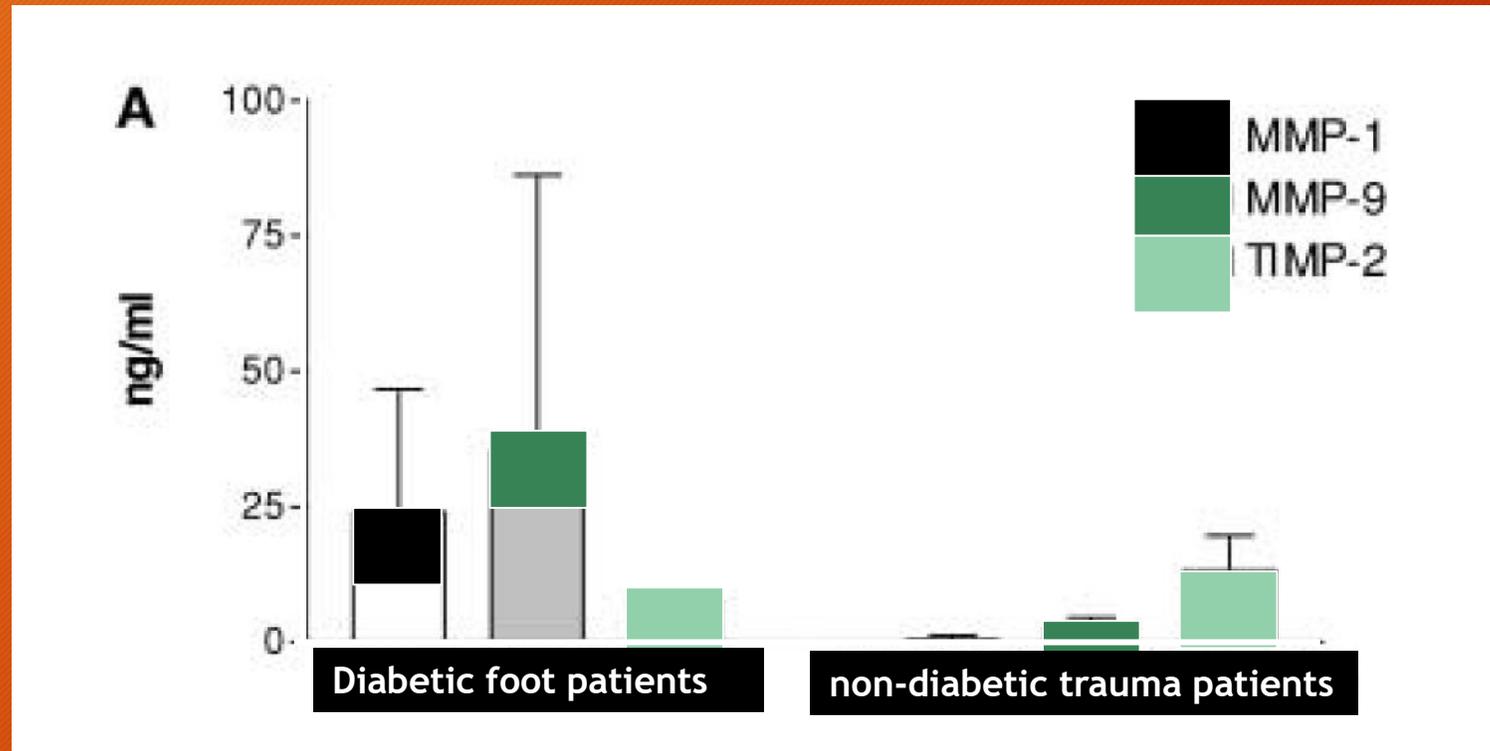


Healing of Pressure Ulcers is Predicted by Protease Activity in Wound Fluids



Ladwig, Robson, Liu, Kuhn, Muir, Schultz.
Ratios of Activated MMP-9/TIMP-1 in Wound
Fluids Are Inversely Correlated With Healing
of Pressure Ulcers. Wound Rep Reg 26-37,
2002.

MMPs in Diabetic Foot Wounds

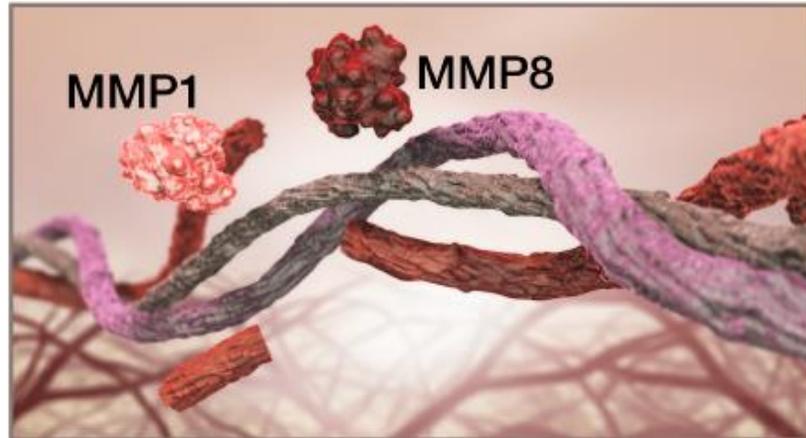


Expression of MMP-1, MMP-9 and TIMP-2

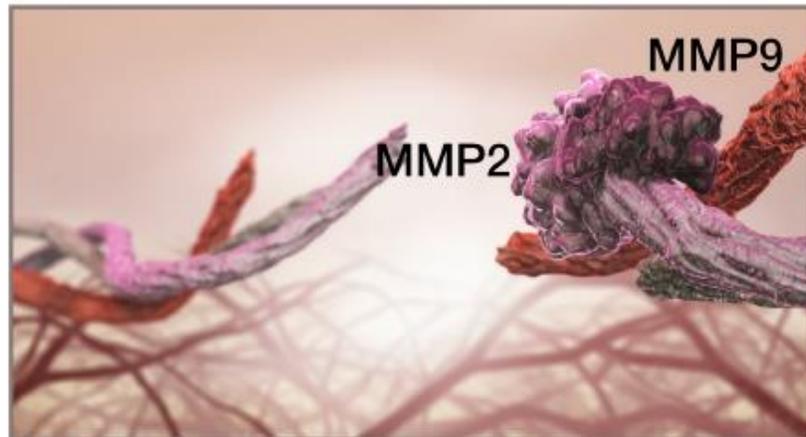
Sequential Degradation of the ECM

Chronic wounds typically show high levels of certain MMPs. These proteases sequentially degrade the native ECM, delaying healing.

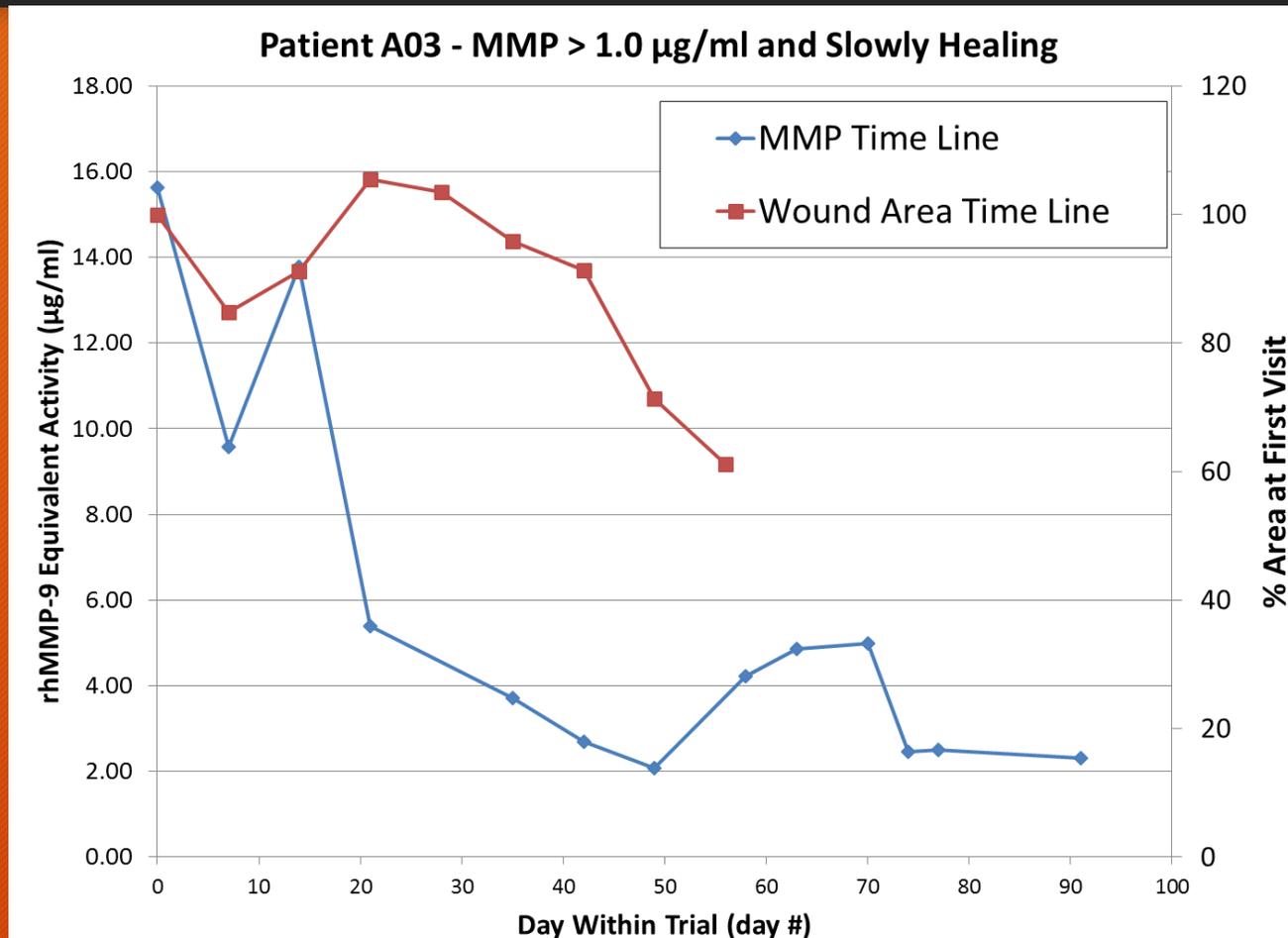
First, collagenases (MMP1 and MMP8) cause the initial breakdown of the vital ECM structure.



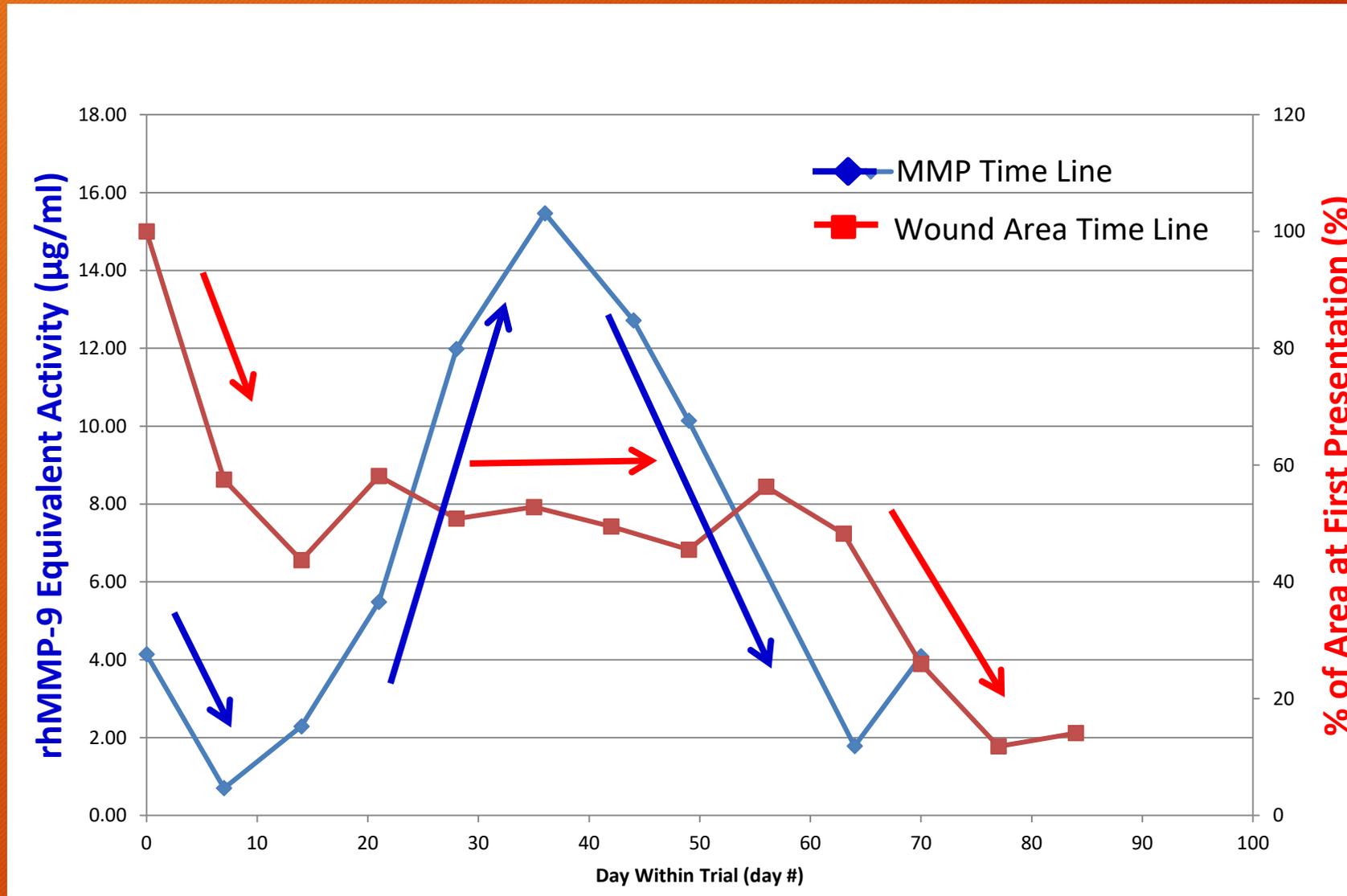
Next, gelatinases (MMP2 and MMP9) further degrade the already-damaged ECM fragments into even smaller components.



MMP Wound Area Ratio

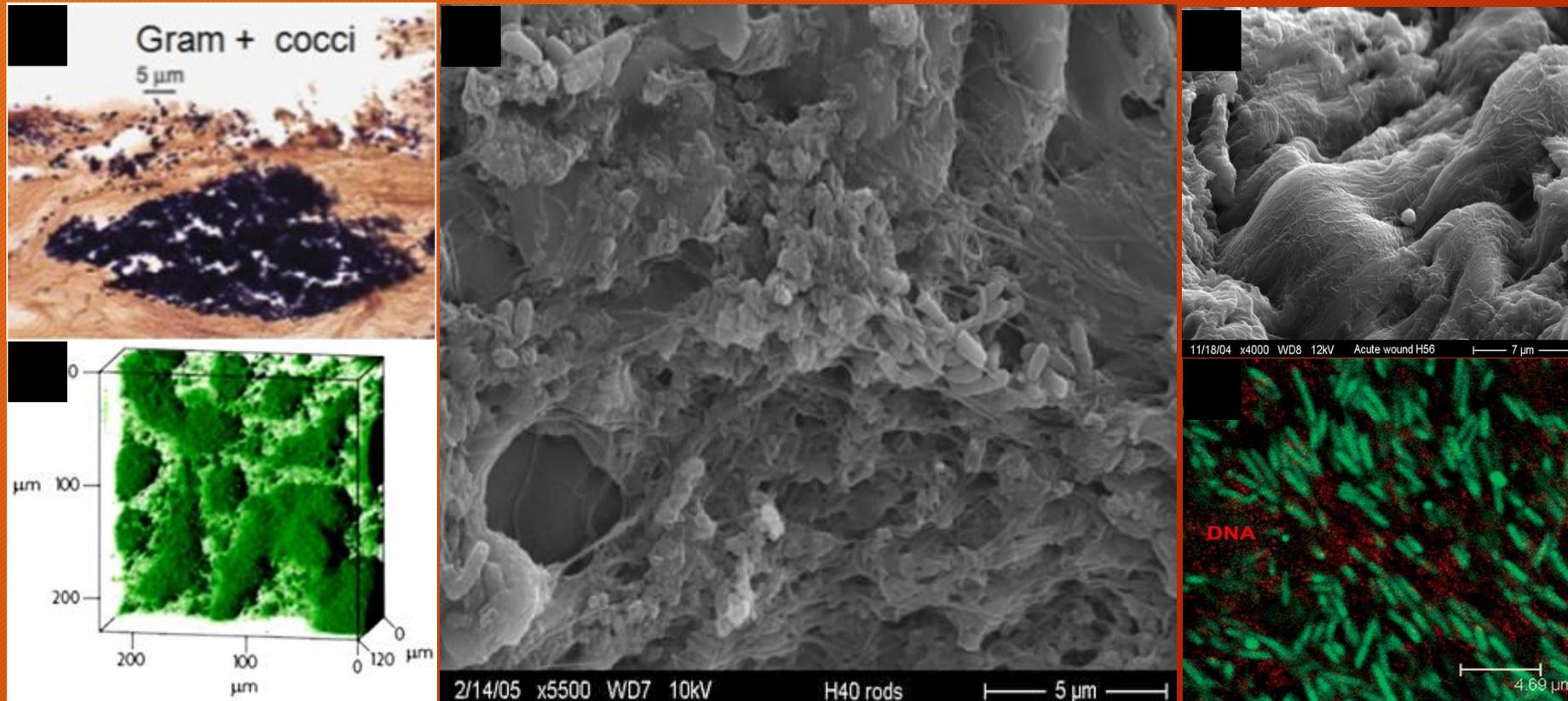


MMP-9 Activity Correlates With Wound Healing Time Course



G. Bohn, B. Liden, G. Schultz, Q. Yang, D.J. Gibson. Ovine-Based Collagen Matrix Dressing: Next-Generation Collagen Dressing for Wound Care. *Advances Wound Care* 6(1):1-6, 2016.

Biofilms Identified in **>80%** of Biopsies of Chronic Wounds but in Only **6%** of Acute Wounds



Panels A, B & C: G. James, E. Swogger, R. Wolcott, E. Pulcini, P. Secor, J. Sestrich, J. Costerton, P. Stewart. *Wound Rep Regen*, 16:37-44, 2008

Panel D: HC Flemming, J Wingender *The Biofilm Matrix*, *Nature Rev Microbiol*, 8:623-633, 2010

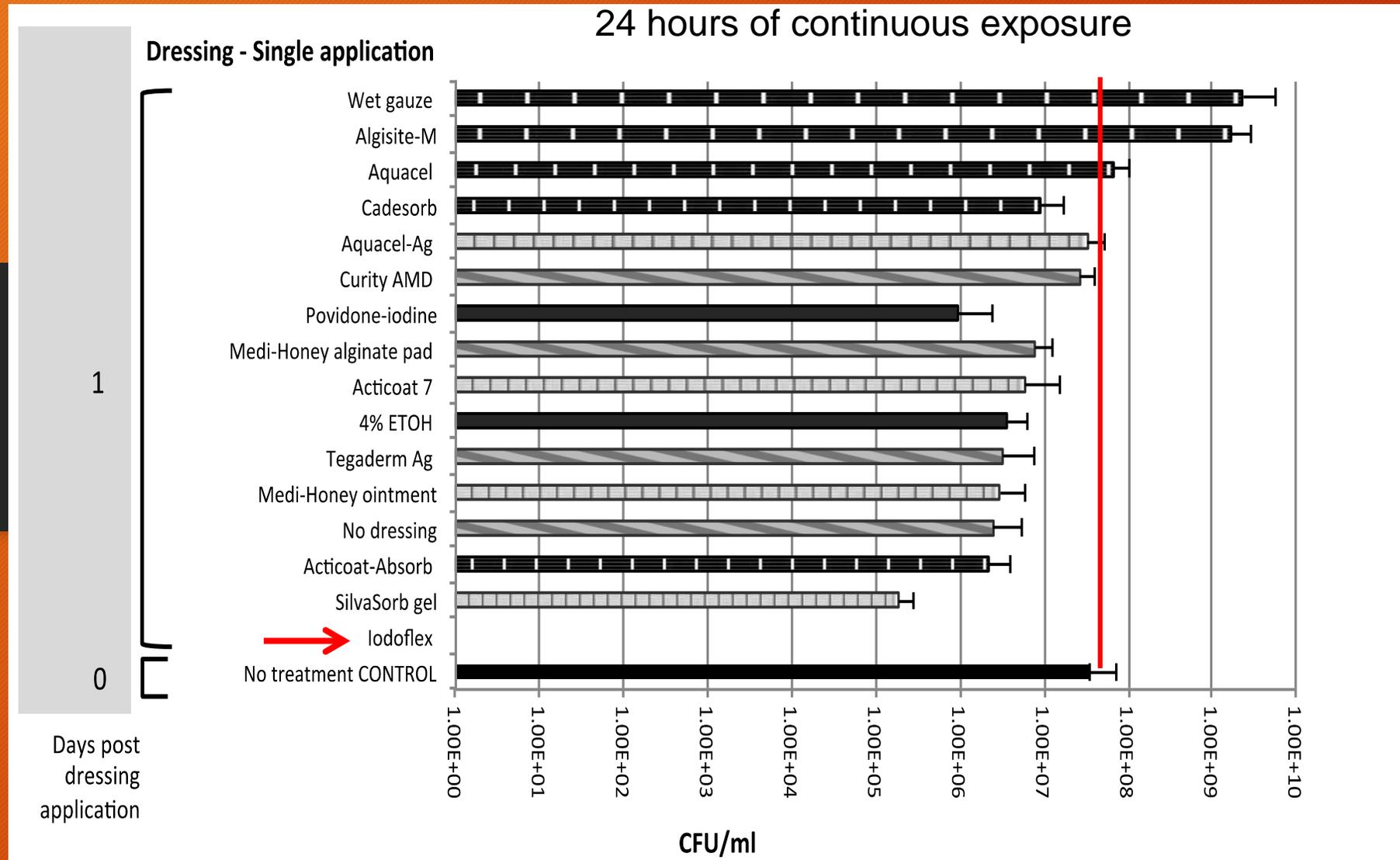
Panel E: SR Schooling, A Hubley, TJ Beveridge. *J Bacteriol* 191:4097-4012, 2009

M. Malone, T. Barjsholt, A. McBain, G. James, P. Stoodley, D. Leaper, M. Tachi, G. Schultz, T. Swanson, R. Wolcott. Prevalence of biofilms in chronic wounds: a systematic review and meta-analysis of published data, *J wound Care*, in press

Question: How do biofilms impair healing of skin wounds?

Answer: Biofilms stimulate chronic inflammation by increasing release of proinflammatory cytokines which leads to highly increased levels of proteases and reactive oxygen species that degrade proteins which are essential for healing.

Effects of Antimicrobial Agents on Mature Biofilms on Pig Skin Explants



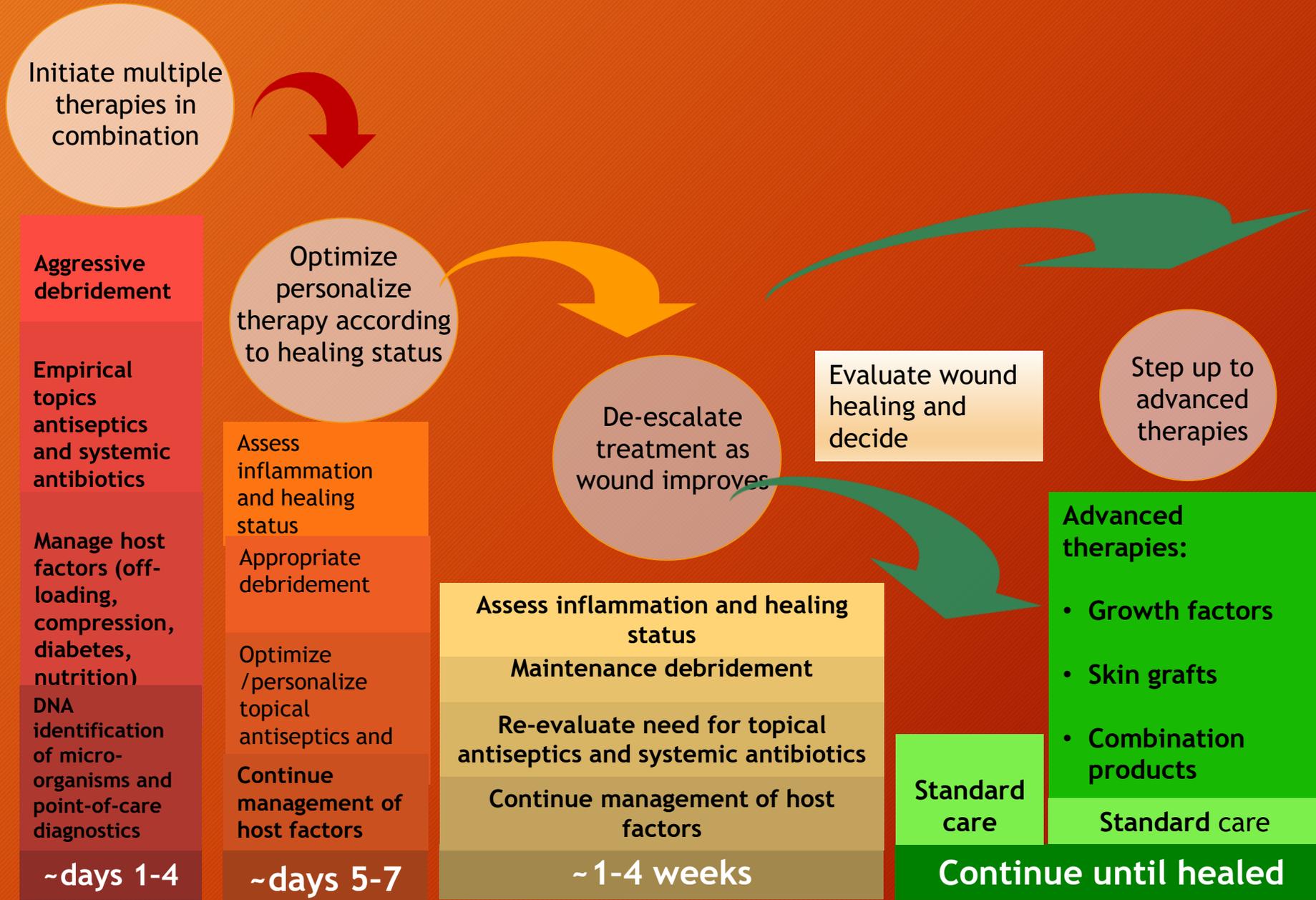
Conclusion: Inflammation in chronic wounds must be reduced to levels that lead to low protease activities which will allow wounds to heal.

Action: Bacterial levels (both planktonic and biofilm) must be reduced for healing

Addressing MMP's in the Wound Bed

- Debridement
- Sacrificial substrate
- Negative pressure
- Sponge effect
- Drugs
- Compression
- TIMP's
- Themselves

Step-Down-Step-Up Treatment for Chronic Wounds



Initiate multiple therapies in combination

Aggressive debridement

Empirical topics antiseptics and systemic antibiotics

Manage host factors (off-loading, compression, diabetes, nutrition) DNA identification of micro-organisms and point-of-care diagnostics

~days 1-4

Optimize personalize therapy according to healing status

Assess inflammation and healing status

Appropriate debridement

Optimize /personalize topical antiseptics and

Continue management of host factors

~days 5-7

De-escalate treatment as wound improves

Assess inflammation and healing status

Maintenance debridement

Re-evaluate need for topical antiseptics and systemic antibiotics

Continue management of host factors

~1-4 weeks

Evaluate wound healing and decide

Step up to advanced therapies

Advanced therapies:

- Growth factors
- Skin grafts
- Combination products

Standard care

Standard care

Continue until healed

New Research Confusing / Complicated

- A trial showed **COLLAGEN** may not reduce MMP activity
- In vitro proteinases rapidly lose activity, likely due **AUTOLYSIS**
 - Introduction of protein **PROTECTS** the proteinases and increase half-life
- Competitive inhibition via protein **IS NOT** supported by this study
- MMP activity **CAN PREDICT FAILURE** of progression week to week
- Proteinases are **NOT THE ONLY** source of failure

Conclusion

- Must address **PLANKTONIC BACTERIA AND BIOFILM**
 - Planktonic
 - BIOFILM
- A severe impact of **BIOFILM IS TO DRIVE PROTEASE ELEVATION**
 - INFLAMATION
- **UTILIZATION OF MULTIPLE** modalities to lower MMP
 - **COMBINATION THERAPIES**
- Utilization of the **STEP UP → STEP DOWN** treatment protocol

Thank You