Inflammation & Wound Chronicity

Management of the Stalled Wound

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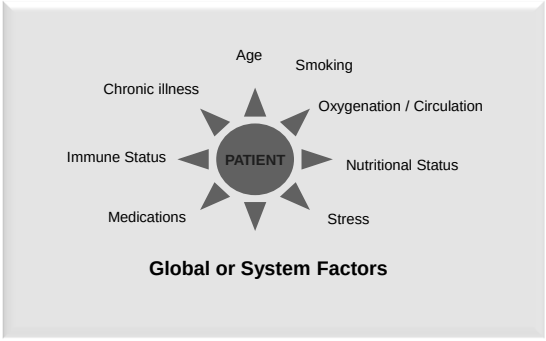
Disclaimer

- RxOS Medical
  - President & CMO
- Acelity
  - Speaker Bureau, Clinical Consultant & Legal Expert

Outline & Overview

- Basic Statistics and Demographics
- Wound Healing Pathophysiology
- Introduction to Inflammation
  - MMPs, Elastases, Proteases
- The Role of the Extracellular Matrix
- Collagen Oxidized Regenerated Cellulose
- Clinical Correlation

Patient Factors Which Impede Healing



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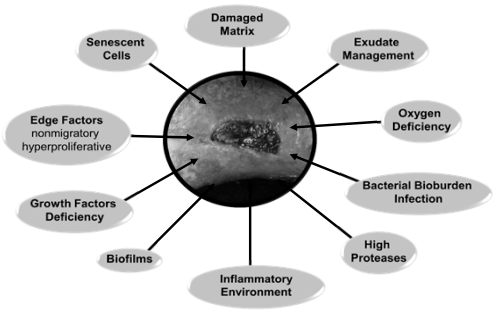
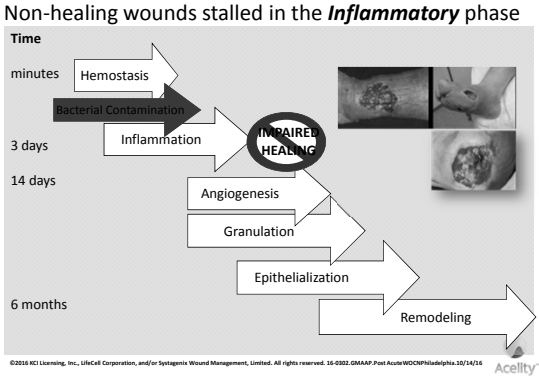
Wound Factors Which Impede Healing



The Wound Healing Continuum

Non-healing wounds stalled in the ***Inflammatory*** phase



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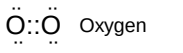
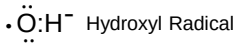
Wound Inflammation Oxidative Stress

Introduction to Free Radical Theory
MMPs, Elastases & Proteases

Oxygen Free Radical

- A free radical is any atom (e.g. oxygen, nitrogen) with at least one unpaired electron in the outermost shell, and is capable of independent existence.
- Free radicals are highly reactive due to the presence of an unpaired electron
- Oxygen Free Radical = Reactive Oxygen Species

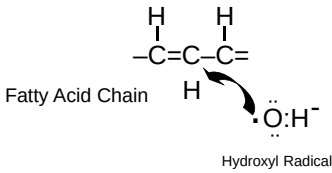




$Fe^{2+} + H_2O_2 \text{ ----> } Fe^{3+} + \cdot OH + OH^-$

ROS Pathophysiology

- Once formed oxygen free radicals seek out electrons to form a stable molecule



ROS Effects & Damage

- **Oxygen Free Radical ATTACK on molecules results in Oxidation Reactions**
  - Lipids (LIPID PEROXIDATION)
  - Amino acids in proteins
  - Enzymes by oxidation of co-factors

Patel RP, T Cornwell, and VM Darley-USMAR: The biochemistry of nitric oxide and peroxynitrite: implications for mitochondrial function. In: Understanding the process of ageing: The roles of mitochondria, free radicals, and antioxidants. (1999) Eds: E Cadenas and L Packer, Marcel Dekker, Inc. NY. Basel 39-40

Oxidative Stress

- **Excessive ROS**
  - Deficient termination reactions
  - Lack of endogenous scavengers / antioxidants
  - Production exceeds reduction reactions

Patel RP, T Cornwell, and VM Darley-USMAR: The biochemistry of nitric oxide and peroxynitrite: implications for mitochondrial function. In: Understanding the process of ageing: The roles of mitochondria, free radicals, and antioxidants. (1999) Eds: E Cadenas and L Packer, Marcel Dekker, Inc. NY. Basel 39-40

Oxidative Stress (Cellular)

- Cell Wall Disturbance (PUFAs)
- Enzyme Disruption
- DNA Damage
- Apoptosis (Cellular Death)
- Tissue Necrosis
- COMPROMISED WOUND HEALING

Lennon SV, Martin SJ, Cotter TG (1991). "Dose-dependent induction of apoptosis in human tumour cell lines by widely diverging stimuli". Cell Prolif. 24 (2): 203–14.

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Wound Healing Physiology

TISSUE REPAIR PHASES

INJURY	HEMATOMA		INFLAMMATION		GRANULATION	REMODELING	TISSUE REPAIR
	Platelet aggregation Haemostasis	Cytokines and Growth factors	Increased vasodilation/ vasopermeability lead to increased exudate Fibrin clots Increased blood flow Phagocytosis	Cytokines and Growth factors	Fibroblast/endothelial cell activation Angiogenesis Collagen synthesis and extracellular matrix formation Wound contracture	Resorption of Type III collagen Orientation of collagen fibers Type I collagen formation	

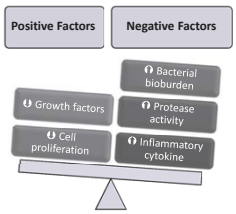
Inflamatory Phase
Respiratory (Oxidative) Burst

- PMNs and Macrophages
- Degradation of internalized particles
- Rapid release of reactive oxygen species (ROS)
- **Formation free radicals…. PROTEASE formation**
- **BACTERIAL KILLING**

Greenhalgh D.G. (1998). The role of apoptosis in wound healing. The International Journal of Biochemistry & Cell Biology 30 (9): 1019–1030.
Muller M.J. , Hollyoak M.A., Moaveni Z., La T., Brown H., Herndon D.N., Heggers J.P. 2003. Retardation of wound healing by silver sulfadiazine is reversed by Aloe vera and nystatin. Burns 29 (8): 834-836.

The Inflammatory Environment

ENVIRONMENT	CHRONIC WOUND	HEALING WOUND
Extra Cellular Matric	Damaged	Functional
Inflammatory Cytokines	High	Low
Protease Activity	Increased / excessive	Low / in balance
Reactive Oxygen Species	Increased	Low
Cell Competence	Senescent	Competent (mitotically)
Metabolic Activity	Low	High



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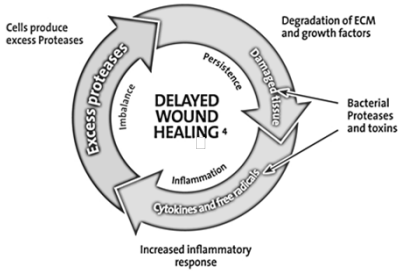
To Kick Start Healing… we must break the cycle

IMBALANCE causes delayed healing!



Cullen Cycle™
Wysocki AB, Staniano-Coico L, Grinelli F. Wound Fluid from Chronic Leg Ulcers Contains Elevated Levels of Metalloproteinases MMP-2 and MMP-9. J Invest Dermatol. 1993; 101;64-68
Harris IR, Yee KC, Walters CE, Cunliffe WJ, Kearney JN, Wood EJ, Ingham E. Cytokine and protease levels in healing and non-healing chronic venous leg ulcers. Exper Dermatol 1995;4:342-349.

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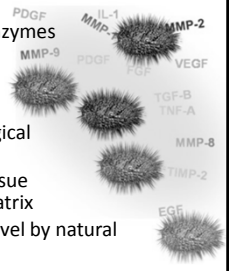
Proteases in Wound Healing

- Proteases are protein-degrading enzymes
- 2 categories of proteases
  - Serine proteases eg. Elastase
  - Matrix metalloproteases eg. MMPs
- Function optimally under physiological conditions
- Collectively, can degrade all soft tissue components of the extracellular matrix
- Normally controlled at the tissue level by natural inhibitors
  - eg. TIMPs, AAT
- Synthesised and stored as inactive pro-enzymes



Armstrong DG, Jude E, The Role of Matrix Metalloproteinases in Wound Healing. *Journal of the American Podiatric Medical Association* Volume 92 Number 1 12-18 2002 Ovington LG, Overview of matrix metalloprotease modulation and growth factor protection in wound healing. Ostomy Wound Manage. 2002 Jun;48(6 Suppl):3-7. Nwomeh BC, Yager DR, Cohen IK. Physiology of the chronic wound. Clin Plast Surg. 1998 Jul;25(3):341-56.

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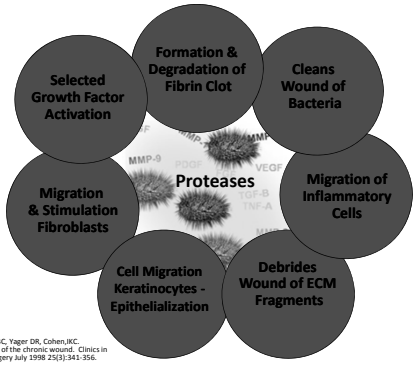
Role of Proteases in Wound Healing



Nwomeh BC, Yager DR, Cohen,IKC.
Physiology of the chronic wound. Clinics in Plastic Surgery July 1998 25(3):341-356.

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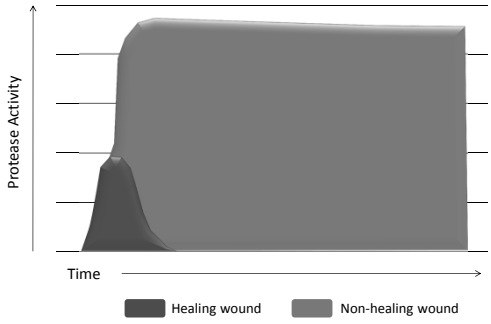
Proteases in Chronic Wounds



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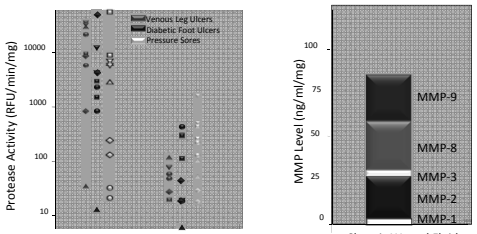
Proteases in Chronic Wounds

Proteases are in EXCESS in Chronic Wounds

Inflammatory Proteases Predominate



Published Data: Cullen, B. et al., (2002) Wound Rep Reg. 10: 16-25

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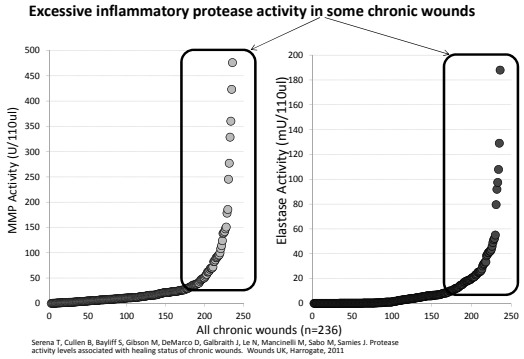
Clinical Range of Protease Activity

Excessive inflammatory protease activity in some chronic wounds



Serena T, Cullen B, Bayliff S, Gibson M, DeMarco D, Galbraith J, Le N, Mancinelli M, Sabo M, Samies J. Protease activity levels associated with healing status of chronic wounds. Wounds UK, Harrogate, 2011

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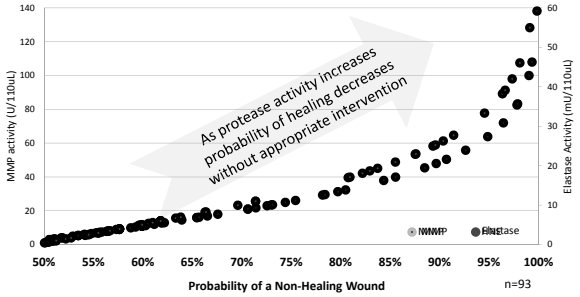
Healing Probability Decreases with Excess Proteases



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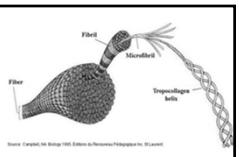
Collagen



- Collagen is a family of proteins
- There are > 20 known different collagen types
- Found in all groups of animals & highly conserved between species
- Is most abundant protein in animals
  - 1/3 of total protein = Collagen
- Traditionally, collagen is sourced from the major domestic breeds such as cow, pig, sheep, deer
  - jelly fish, fish and chicken feet collagens available

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Collagen in Skin

- Collagen comprises more than 25% of total protein
- It is the major component of soft tissue including dermis (skin)
- Collagen is made up of 3 proteins wrapped around each other to form a triple helix (rope like structure)
  - Types I and III, are predominant in skin
  - Type I has 2 different protein chains
  - Type III has 3 copies of the same protein chain

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Benefits of Collagen

- Collagen is a natural occurring material
- It is a component of tissue
- It is "recognized" by tissue cells
  - Enhances the deposition of new collagen fibres
  - Substrate for cellular adhesion and migration
- It is bioresorbable/biodegradable
  - Peptides & amino acids can be reused by cells
  - Collagen proteins & peptides stimulate cells
  - Chemotactic for neutrophils, macrophages, and fibroblasts
- Low inflammatory & antigenic response
- Hemostatic properties
- Can act as a sacrificial substrate for excessive MMPs

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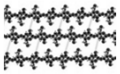
Oxidized Regenerated Cellulose (ORC)

- Cellulose is the most abundant material on the surface of earth
- Cellulose is mainly obtained from wood pulp and cotton

- Chemical modification of cellulose – different properties
- Oxidation makes cellulose biodegradable - ORC
- Degrades in a predictable & consistent manner
- Degradation occurs by fluid absorption & subsequent gelling
- ORC degrades to sugars (glucose & glucuronic acid)

- Used in SURGICEL® as hemostat (Johnson & Johnson)
- Used in INTERCEED® as adhesion barrier (Johnson & Johnson)





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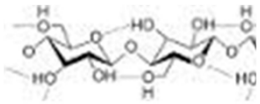
Benefits of ORC

- ORC degrades to sugars (glucose & glucuronic acid)
  - with exposure to wound fluid
  - sugars provides source of energy or nutrients
- ORC lowers pH as it breaks down which helps control bacterial growth
- Studies in vitro have shown that ORC
  - Stimulates cell growth
  - Provides growth factor protection
- Inactivates proteases such as Elastase
- Hemostatic properties

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Collagen/ORC – Published Data

- Published studies have shown that Collagen and ORC are biomaterials which help rebalance the chronic wound environment

Published In Vitro studies show:
- Combination of Collagen, ORC (& Silver)
  - Binds and inactivates proteases
    - MMPs, Elastase, Bacterial proteases
  - Reduces bacterial bioburden
  - Increases cell growth
  - Protects growth factors

Published Clinical studies show:
- Improves clinical outcomes

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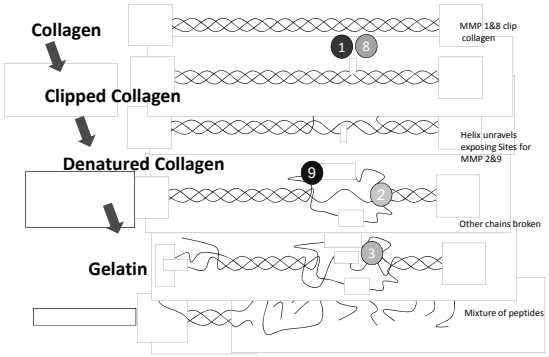
Collagen a Sacrificial Substrate for Multiple MMPs



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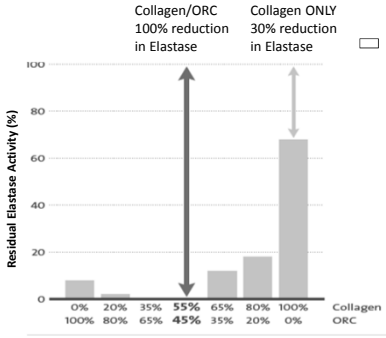
ORC Reduces Elastase Activity



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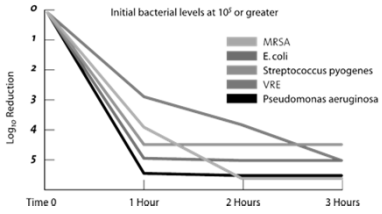
Collagen/ORC/Silver
Benefits of Silver Without Harming Cell Growth

Antimicrobial data comparable to other silver dressings



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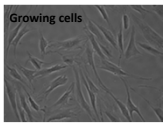
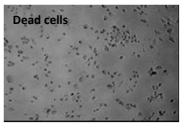
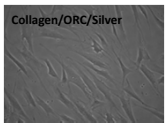
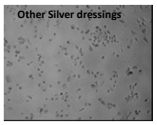
Collagen/ORC/Silver
Benefits of Silver Without Harming Cell Growth

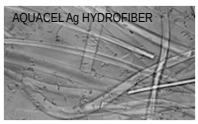
The only silver containing dressing to enhance cell growth











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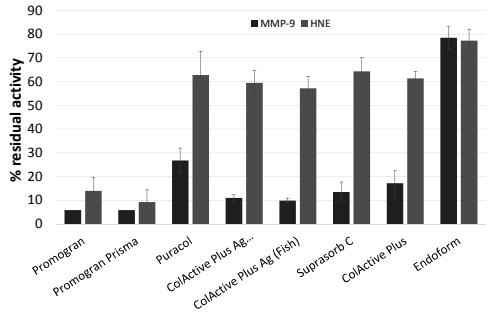
In Vitro Studies Show Collagen/ORC Provides Unsurpassed Reduction in Protease Activity



Published at EWMA 2015. Can natural materials be adapted to optimise their efficacy in wound care Gibson M, Cullen B.

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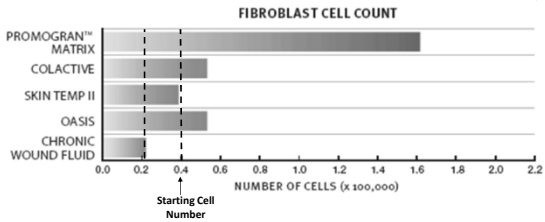
Collagen/ORC Effect on Cell Growth (CWF in Vitro)

PROMOGRAN™ outperformed collagen dressings in overcoming the negative effects of chronic wound fluid on cell growth



Same effect observed with keratinocytes and endothelial cells

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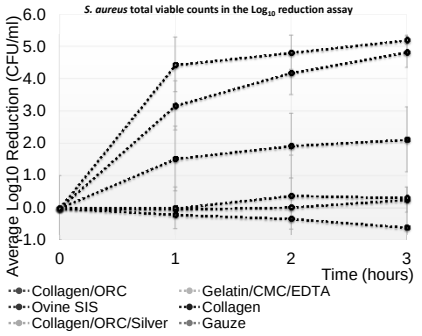
Collagen/ORC
Effective in Reducing Bacterial Bioburden



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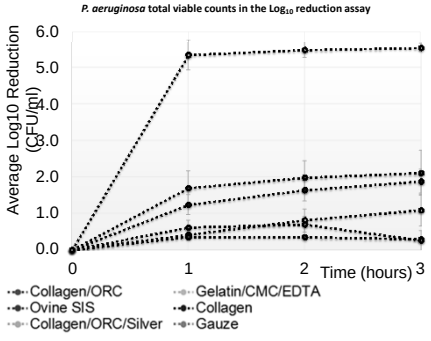
Collagen/ORC/Silver
Effective Control of P. aeruginosa



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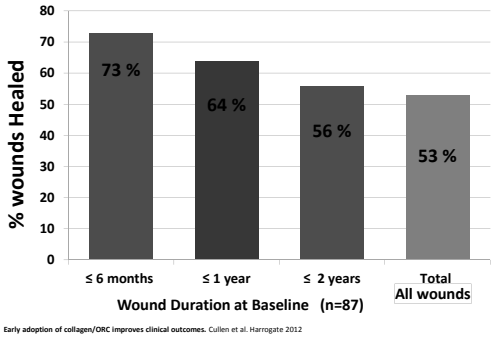
Collagen/ORC
Early Treatment Improves Healing



Early adoption of collagen/ORC improves clinical outcomes. Cullen et al. Harrogate 2012

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Clinical Correlation

Technical Pearls and TIPS

- Early utilization especially with wound inflammation
- Mandatory attention to basic wound care
- Meticulous wound bed preparation
- Suitable transition from NPWT
- Appropriate for tunneling, undermining and depth
- Complimentary to HBOT

CHALLENGES TO SUCCESS

- Clinician knowledge of wound physiology
- Understanding the science behind the technology
- Recognition of the “Inflammatory Wound”
- Discrimination between the “Infected Wound” and the “Inflammatory Wound”

In Summary

Collagen/ORC publications have shown
- Reduces protease activity in wounds
- Clinically effective in treating chronic wound

Collagen/ORC
- Provides an optimal environment which promotes wound healing
- Early adoption significantly improves outcomes

Collagen/ORC/ Silver
- Delivers the benefits of silver and protects against infection

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Thank You…

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