



# Oxygen Free Radical Binding Technology Promotes Wound Healing

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Thursday, July 30<sup>th</sup>, 2009

Track 1 – Advances in Wound Care and Dermatology



# Disclaimer

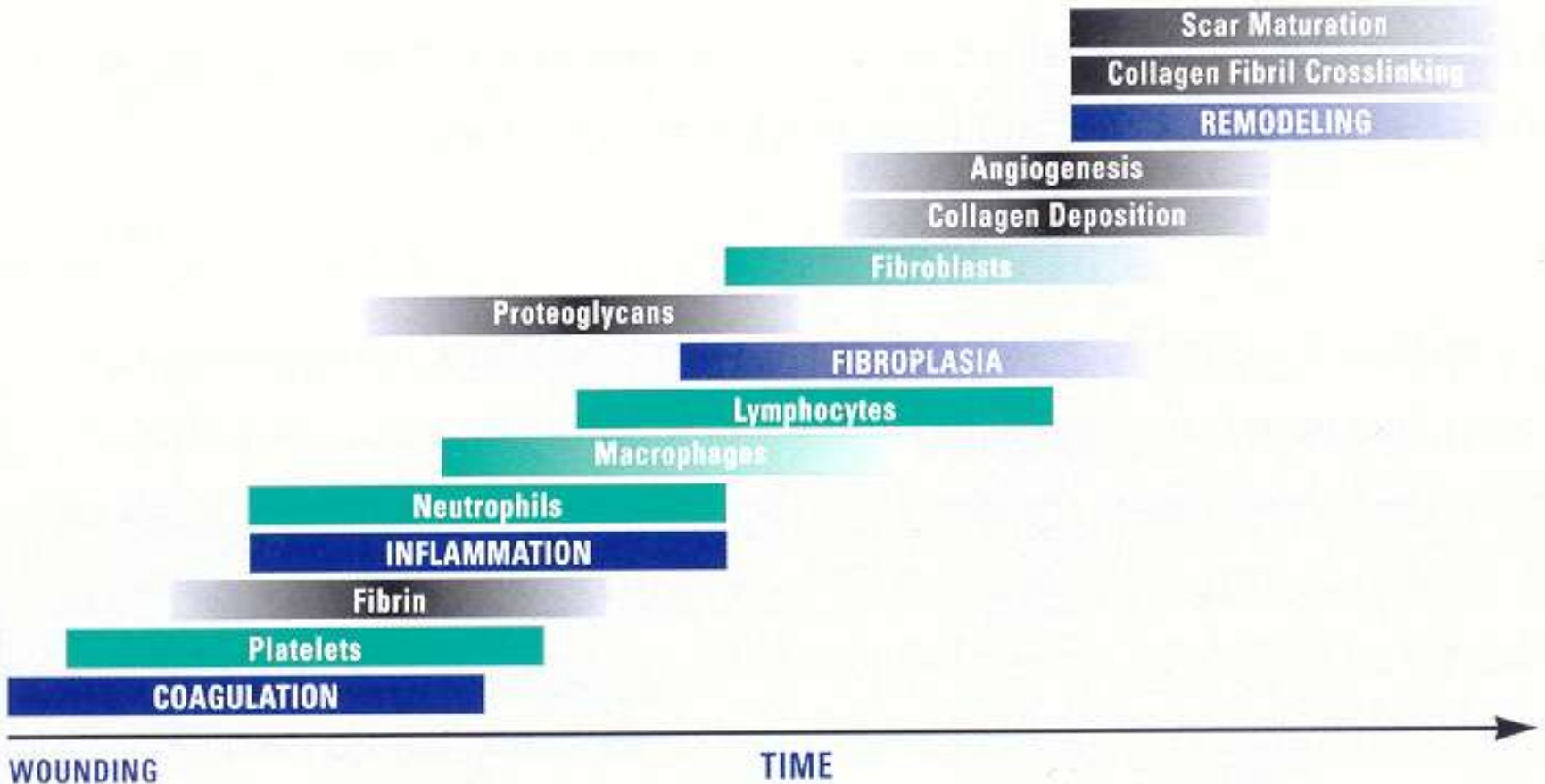
- Director of Board of Medical Advisors
  - Consultant
- Wake Pharma, US Inc.
- Wound- Be- Gone



# Wound Healing

- Precise cellular interaction
- Coordinated chemical signalling
- Predicted protein synthesis

# Wound Healing Physiology



# Wound Healing Physiology

## TISSUE REPAIR PHASES

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



# Hemostatic Phase

- Platelets
  - ECM proteins, Cytokines / Growth factors
  - Proinflammatory Mediators
    - Serotonin, Bradykinin
    - Prostaglandins, Prostacyclin
    - Thromboxane, Histamine
  - Action
    - Cellular Proliferation
    - Vasodilation
    - Vasogenic Edema

# Inflammatory Phase

- Polymorphonuclear Neutrophils (PMN)
  - attracted by fibronectin, growth factors, kinins
- Action
  - phagocytize debris and bacteria
  - kill bacteria
    - free radicals
    - **respiratory or oxidative burst**
  - cleanse the wound by secreting proteases

# Respiratory (Oxidative) Burst

- Formation free radicals
- Rapid release of reactive oxygen species
  - ROS
  - superoxide radical and hydrogen peroxide
- PMNs and Macrophages
- Degradation of internalized particles
- 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., Heggors J.P. 2003. Retardation of wound healing by silver sulfadiazine is reversed by Aloe vera and nystatin. *Burns* 29 (8): 834-836.

# Bacterial Killing Mechanisms

- Superoxide and other ROS are capable of killing bacteria and fungi by mechanisms that are not yet fully understood
  - inactivate critical metabolic enzymes
  - initiate lipid peroxidation
  - liberate redox active iron, which allows the generation of indiscriminate oxidants such as the hydroxyl radical
  - virulence of many pathogens is dramatically attenuated when their superoxide dismutase (SOD) genes are deleted.

# ROS Collateral Damage

- Superoxide anion, peroxynitrite, and other reactive oxygen species
  - over load existing scavenger systems
  - peroxidation of proteins and lipids
  - protein nitrosylation
- Superoxide reacts with NO resulting in the formation of peroxynitrite
  - reducing the bioactive NO needed to dilate terminal arterioles, feed arteries and resistance arteries

Biochemistry Basics

# **FREE RADICAL INTRODUCTION**



# Free Radical

- By definition 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 Radicals

- Any free radical involving oxygen
- Reactive Oxygen Species (ROS)
  - Hydroxyl radical ( $\text{OH}\cdot$ )
  - Superoxide Anion ( $\text{O}_2\cdot^-$ )
  - Singlet oxygen
  - Ozone ( $\text{O}_3$ )
  - Hydrogen peroxide ( $\text{H}_2\text{O}_2$ )
  - Nitric Oxide: Peroxynitrite ( $\text{ONOO}^-$ )
  - Carbon Based: Peroxyl Radicals ( $\cdot\text{O}_2\text{C}$ )
  - Thiol compounds ( $\text{RSO}_2\cdot$ )

# ROS Effects & Damage

- Oxidative “Stress”
- Oxidations of polyunsaturated fatty acids in lipids (lipid peroxidation)
- Oxidations of amino acids in proteins
- Oxidatively inactivate specific enzymes by oxidation of co-factors
- Damage of DNA
- Cellular Apoptosis

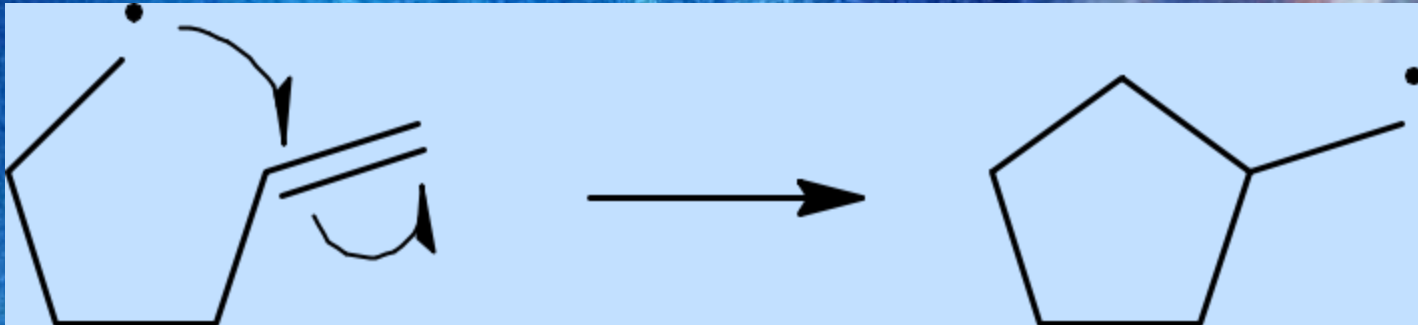
# Polyunsaturated Fatty Acids

- Polyunsaturated fatty acids (PUFAs) are abundant in cellular membranes and in low-density lipoproteins (LDL) and allow for fluidity of cellular membranes

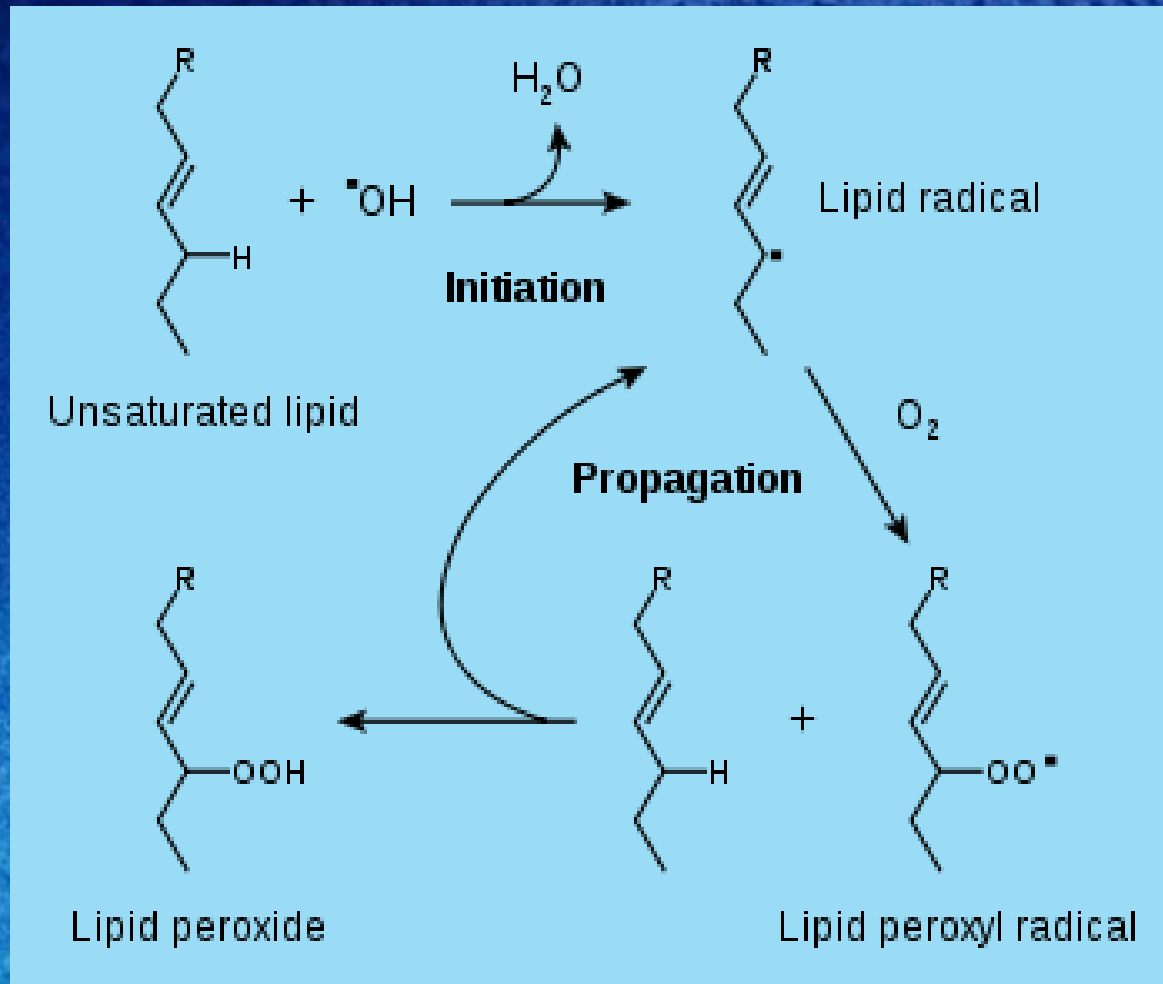


# Lipid Peroxidation

- Oxygen free radicals prefer to steal electrons from the lipid membrane (PUFAs), initiating a free radical attack on the cell known as lipid peroxidation. Reactive oxygen species target the carbon-carbon double bond of polyunsaturated fatty acids.



# Lipid Peroxidation



# Chain Reactions

- **Initiation:** reactions are those which result in a net increase in the number of free radicals.
- **Propagation:** Reactions are those reactions involving free radicals in which the total number of free radicals remains the same.
- **Termination:** Reactions are those reactions resulting in a net decrease in the number of free radicals. Typically two free radicals combine to form a more stable species.

# Oxidative Stress (Systemic)

- Atherosclerosis
- Parkinson's disease
- Heart Failure
- Myocardial Infarction
- Alzheimer's disease
- Chronic fatigue syndrome
- Aging

# Oxidative Stress (Cellular)

- DNA Damage
- Cell Wall Disturbance (PUFAs)
- Enzyme Disruption
- Apoptosis
- Tissue Necrosis

# Antioxidant Defenses

- Antioxidants are effective because they give up their own electrons to free radicals
- ROS are stabilized and lipid peroxidation ceases and the chain reaction of oxidation is broken
- Antioxidant becomes a free radical by definition, but are not harmful as they have the ability to accommodate the change in electrons without becoming reactive

# Antioxidants

- Vitamin E
- Beta-carotene
- Coenzyme Q
- Intracellular Antioxidant Scavengers
  - vitamin C
  - glutathione peroxidase
  - superoxide dismutase (SD)
  - catalase

# Steric Hindrance

- Steric hindrance or steric resistance occurs when the size of groups within a molecule prevents chemical reactions that are observed in related smaller molecules.
- Free Radical Traps
- End ROS chain reactions via termination

# Applications in Wound Care

- Wound Be Gone
  - Development and Patent
  - Company History and Background
  - Description of Technology
    - Hydrogel
    - Sterically hindered amine groups



# Development and Patent

- Institute of Macromolecular Chemistry
  - Academy of Sciences of the Czech Republic
    - Founded 1959
  - Professor Otto Wichterle
    - Macromolecules & Polymer Chemistry
    - Discovery of soft contact and intraocular lenses.

# Development and Patent

- Jirí Labský, PhD
- Jirí Vacík, PhD
  - Hydrogel Chemistry
  - Sterically Hindered Amines
- Pavel Hošek, MD
  - Clinical Validation



## Preparation for prevention and healing of inflammation affections

**Abstract**

A preparation for prevention and healing of inflammation affections comprising in an amount of 0.1 to 99.9% by weight derivatives of sterically hindered amines selected from the group consisting of: soluble polymers or copolymers prepared by radical polymerization in the presence of 0.01 to 10% by weight, of initiators prepared in a polymerization mixture comprising individually or in combination an aliphatic amine monomer of the general formula (A), soluble polymers or copolymers prepared by radical polymerization in the presence of 0.01 to 10% by weight of initiators from monomers of cyclic sterically hindered amines of the general formula (B), soluble polymers prepared by polycondensation of difunctional sterically hindered amines of the general formula (F), soluble polymers or copolymers prepared by polycondensation of difunctional cyclic sterically hindered amines of the general formula (G), soluble copolymers prepared by polycondensation of difunctional cyclic, sterically hindered amines of the general formula (G) and monofunctional cyclic sterically hindered amines in an amount of 0.1 to 15% by weight, based on the total polymerization mixture, of the general formula (H), derivatives of sterically hindered cyclic amines of the general formula (O), polymers, copolymers, or natural compounds comprising free reactive groups --OH, --NH.sub.2, --COOH, --CHO, oxiranyl, selected from the group poly(vinyl alcohol), cellulose, (2-hydroxyethyl)cellulose, (carboxymethyl)cellulose, agar derivatives, polymers obtained by condensation, using alkanediol derivatives, oligomers and polymers of ethylene glycol or propylene glycol, natural or synthetic polymers, comprising a free carboxyl group, amino group or aldehyde group, prepared by additional functionalization of polymers or natural compounds by polymeranalogous reaction with a suitable sterically hindered amine.

Inventors: **Labsky ; Jiri (Praha, CZ), Vacik; Jiri (Praha, CZ), Hosek; Pavel (Karlovy Vary, CZ)**  
Assignee: **Institute of Macromolecular Chemistry (Prague, CZ)**  
Appl. No.: **09/555,626**  
Filed: **July 27, 2000**  
PCT Filed: **October 02, 1998**  
PCT No.: **PCT/CZ98/00046**  
PCT Pub. No.: **WO99/28359**  
PCT Pub. Date: **June 10, 1999**

**Foreign Application Priority Data**

Dec 03, 1997 [CZ]

3867-97

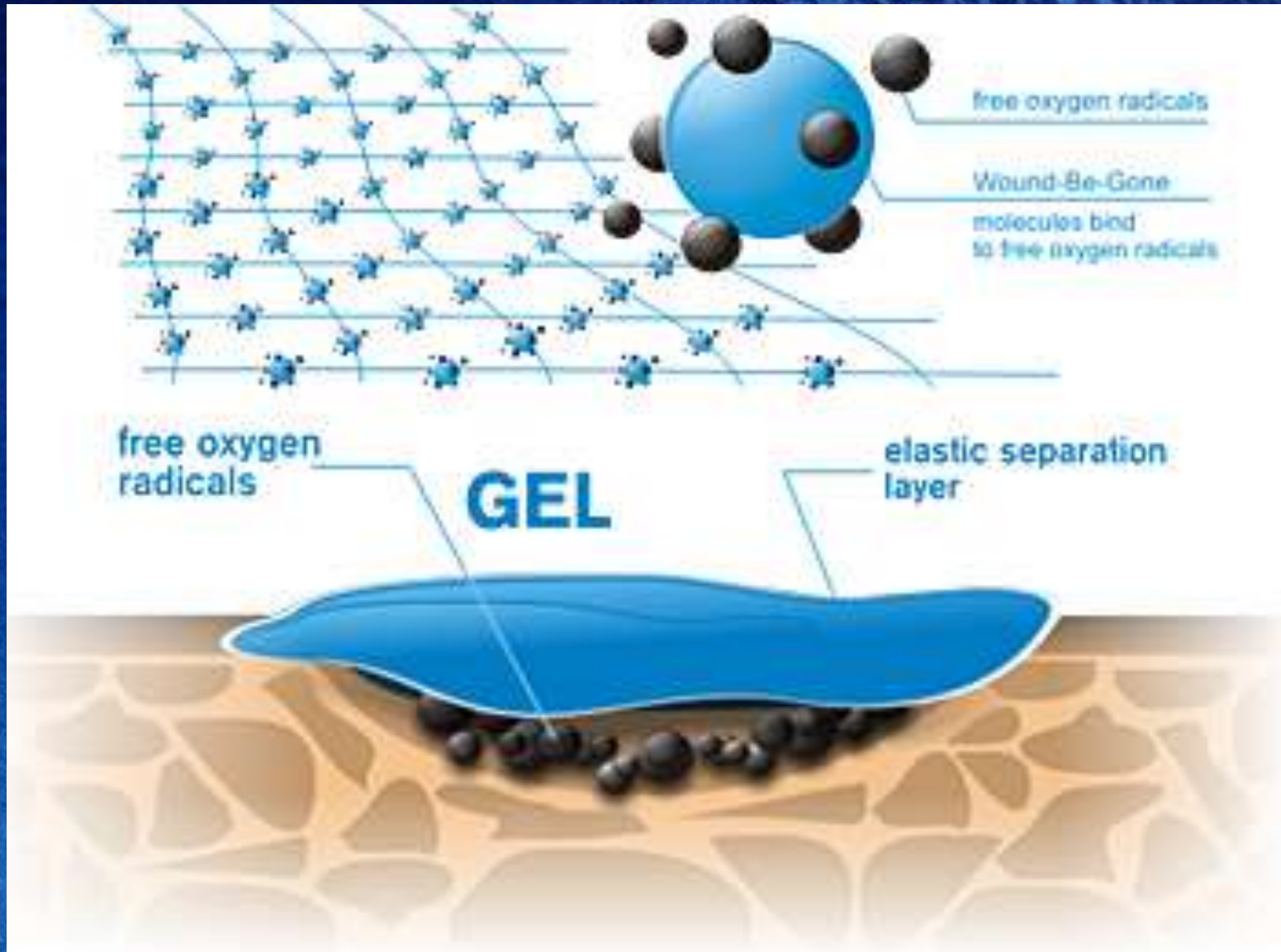
# Product Description

Wound-Be-Gone is available in two tube sizes:

- 5 gram
- 30 gram



# Mechanism of Action



# Indications

- Minor Injuries (not requiring medical attention):
  - Cuts
  - Scratches
  - Scrapes
  - Insect bites
  - Blisters



# Indications

- Acute Wounds
  - Lacerations
  - Abrasions
  - Burns
  - Punctures
  - Traumatic Wounds
  - Surgical Incisions



# Indications

- Chronic Wounds:
  - Diabetic Foot Ulcers
  - Arterial Ulcers
  - Venous Insufficiency Ulcers
  - Pressure Ulcers
  - Surgical Wounds
  - Skin Tears



# WBG - Clinical Application



# WBG - Clinical Application



# WBG - Clinical Application



# Case Studies

- WM, a 35 year old male with past medical history of DM, HTN, and morbid obesity
- Since 2005 DFUs, right hallux amputation, and Charcot foot
- 1/28/09 RLE abscess and NSTI
- Surgical Debridement, NPWT, ABX
- NPWT D/C'd 2-19-09
- WBG Initiated

2-29-09



Courtesy: David A. Yeager, D.P.M and Brandon R. Gumbiner, DPM, C. Ped.

**3-11-09**



Courtesy: David A. Yeager, D.P.M and Brandon R. Gumbiner, DPM, C. Ped.

4-20-09



Courtesy: David A. Yeager, D.P.M and Brandon R. Gumbiner, DPM, C. Ped.

5-26-09



Courtesy: David A. Yeager, D.P.M and Brandon R. Gumbiner, DPM, C. Ped.

# Case Study 2

- HH, a 36 year old female
  - Unremarkable PMH
  - Smoker ½ pack per day
- 11/2008 sustained an acute open fracture of her RD5 with disarticulation of the DIP
  - initially managed with lavage and delayed primary closure
  - post-operative complications & osteomyelitis of the RD5, digit amputation (3/13/09)
  - WBG initiated 3-27-09

**3-27-09**



Courtesy: David A. Yeager, D.P.M and Brandon R. Gumbiner, DPM, C. Ped.

4-1-09



4-10-09



Courtesy: David A. Yeager, D.P.M and Brandon R. Gumbiner, DPM, C. Ped.

# Case Study 3

- MK, a 64 year old patient with DM and PAD
  - admitted for an infected diabetic foot ulcer
  - surgical débridement and ABX
  - postoperatively HBOT and NPWT (9-5-08)
  - NPWT was D/C'd (9-26-08)
  - WBG Initiated

9-5-08



9-26-08



10-13-08



11-14-08



# Case Study 4

- TZ, a 73 year old patient
  - presented for initial wound care consultation in early 2008
  - diagnosed with venous insufficiency and after vascular evaluation
  - started on compression therapy and topical silver
  - wound showed slow progress after 6 months of standard care
  - WBG initiated 11-17-08

9-15-08



11-17-08



12-22-08



# Wake Pharma US, Inc

- Wake Pharma US Founded 2007
  - 2226 Landemire Rd
  - Elk Grove Village, IL 60007
- Initial Importer and Exclusive Distribution:
  - USA, Canada, South America
- E-mail: [info@wakepharmaus.com](mailto:info@wakepharmaus.com)
- Web: [www.wakepharmaus.com](http://www.wakepharmaus.com)
- [www.woundbegone.com](http://www.woundbegone.com)

# Conclusion

- ROS can negatively impact wound healing
- Use of “free radical traps” can contain the propagation of ROS
  - Prevent cellular damage
  - Promote wound healing
- Additional research and RCT are indicated

# Thank You

- Wake Pharma US, Inc
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  - [www.wakepharmaus.com](http://www.wakepharmaus.com)

