GREEN FOLDER

The physiological and biochemical mechanisms of action of V.A.C.® Therapy™

Presented by
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Director Clinical Marketing

KCI The Clinical Advantage

THE V.A.C. VACUUM ASSISTED CLOSURE®

Overview

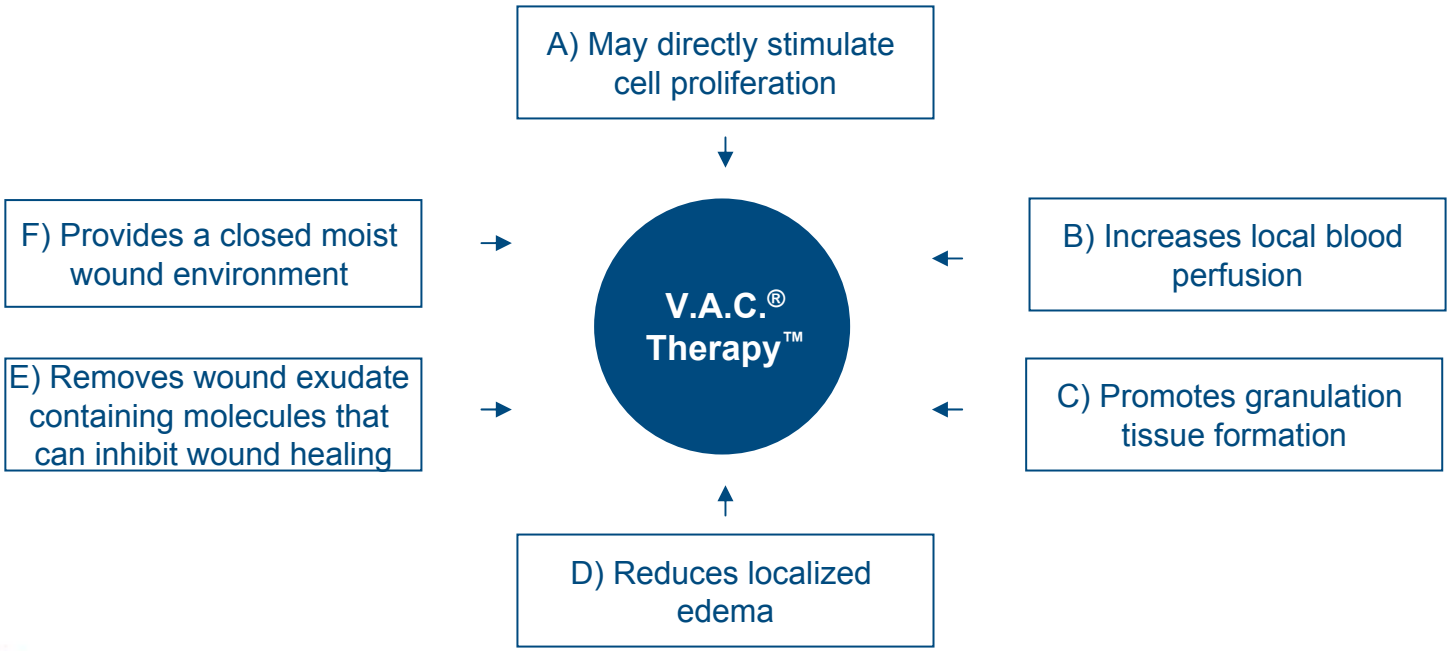
- Summarize experimental evidence for the mechanism of action of V.A.C.® Therapy™
- Published literature
  - Theoretical models
  - In vitro studies
  - Animal experiments
  - Clinical studies
- Key conclusions regarding the role of V.A.C.® Therapy™ in the wound healing process

Chronic versus acute wound healing

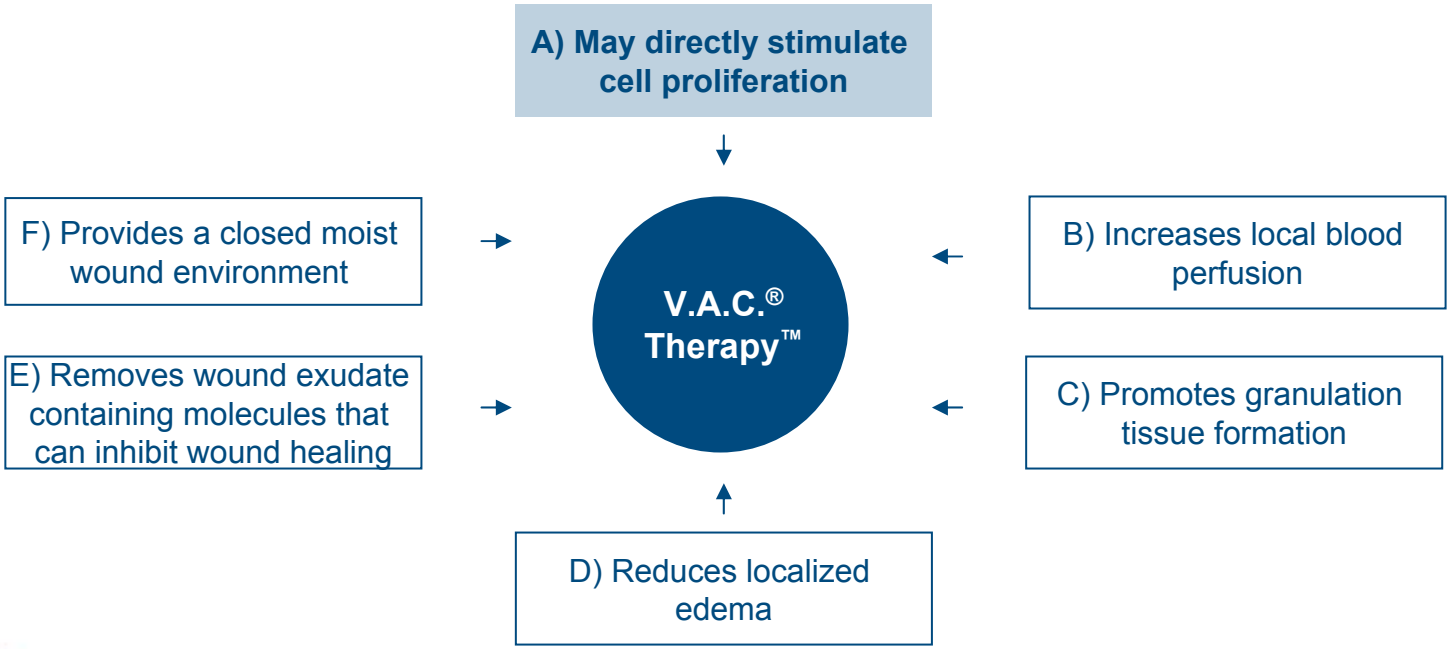
Healing wounds		Chronic wounds
↑	Mitogenic activity	↓
↓	Inflammatory Cytokines	↑
↓	Protease activity	↑
↑	Mitotically competent cells	↓

Teot L, Banwell PE, Ziegler UE, Surgery in Wounds. Springer 2004, 30

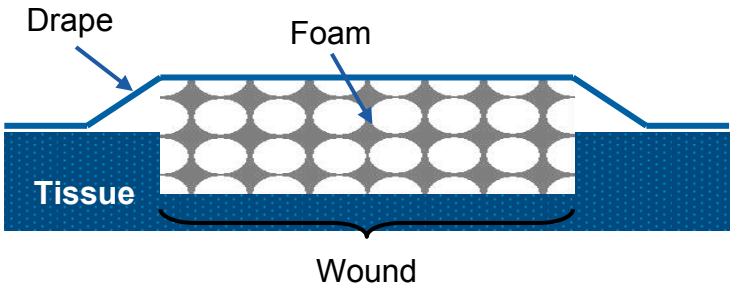
Possible mechanisms of action of V.A.C.® Therapy™



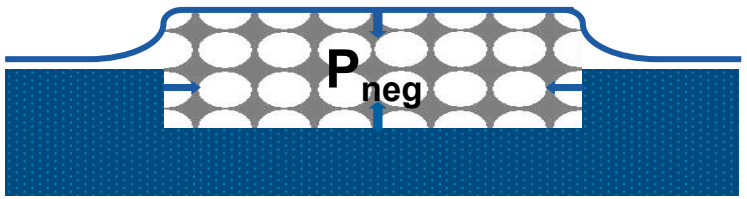
Possible mechanisms of action of V.A.C.® Therapy™



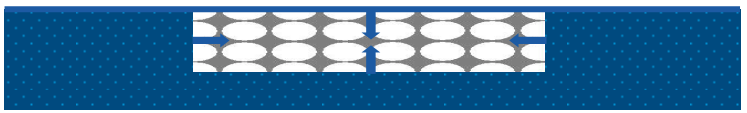
V.A.C.® Therapy™ – Foam/Tissue Interactions, Forces on Tissue Surface



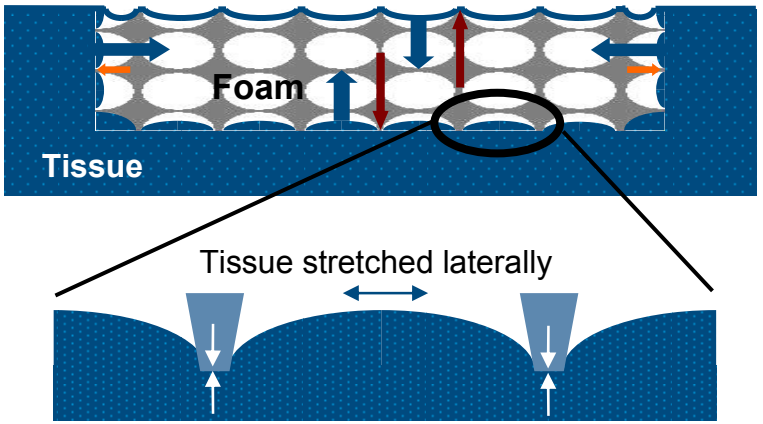
Therapy initiated:



Equilibrium:



Foam/Tissue interactions and Wound Tissue Stretching



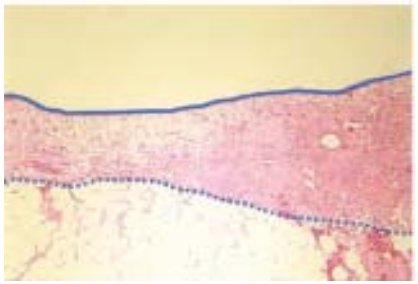
Negative Pressure (Vacuum)

Foam **Normal** Compressive Stress

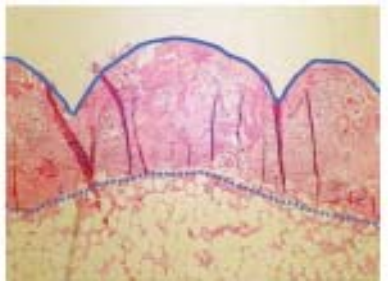
Foam **Lateral** Compressive Stress

V.A.C.® Therapy™ induces microdeformations

- Microdeformations in V.A.C.® treated wounds
- V.A.C.® treated wounds show a rich vascular network compared to control sites without foam



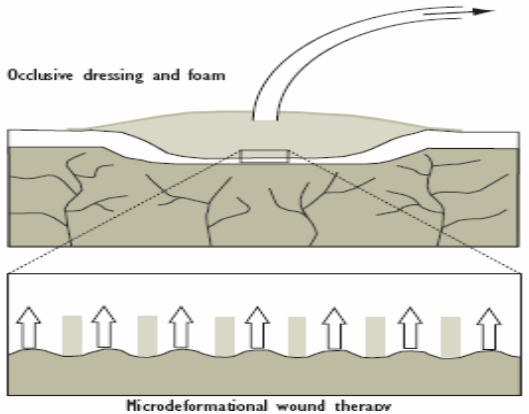
Non-V.A.C.® System (day 7)



V.A.C.® System (day 7)

Saxena V, et al. *Plastic and Reconstructive Surgery,* 2004; 114(5):1086-96.

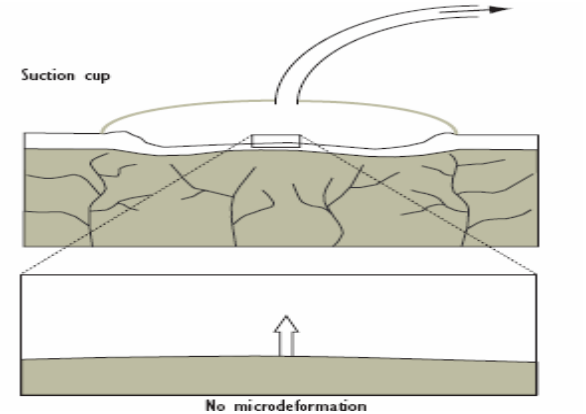
V.A.C.® Therapy™ induces microdeformations



V.A.C.® System

↓

Microdeformation



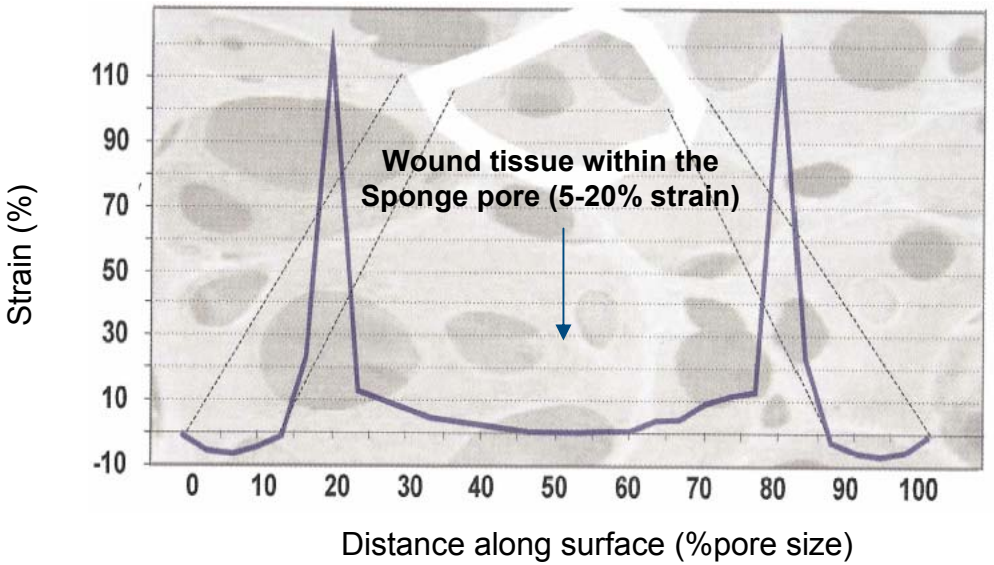
Common suction device

↓

No microdeformation

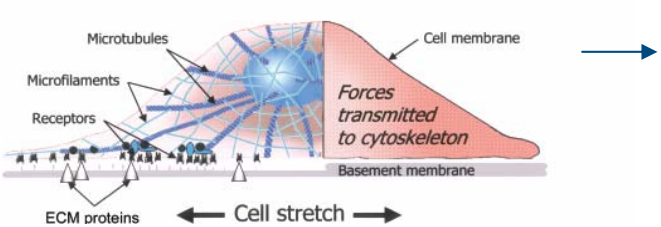
Orgill DP, Bayer LR, Neuwalder J, Felter RC. Business Briefing: Global Surgery – Future Directions 2005, 22-25

V.A.C.® Therapy™ induces wound surface strain in a repeating pattern



Modified Graphic from Willy C, *Die Vakuumtherapie*, May 2005, p86

V.A.C.® Therapy™ may directly stimulate cell proliferation by microdeformations



→

Integrin activated signaling pathways and transmission of mechanical stress

Structural changes in cytoskeleton

Down-regulation of cell cycle inhibitors

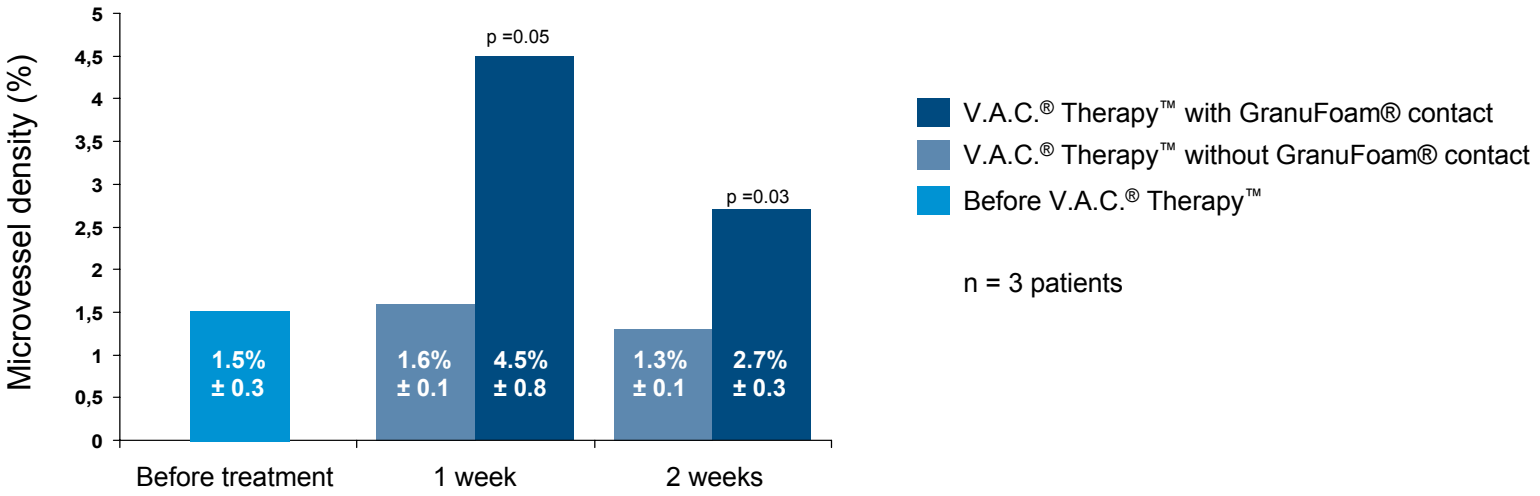
Activate genes required for G1/S transition

→

Fibroblast proliferation and angiogenesis

Saxena V, et al. Plastic and Reconstructive Surgery, 2004; 114(5):1086-96. Huang S, Chen CS, Ingber DE. Mol Biol Cell. 1998 Nov;9(11):3179-93. Danciu TE, Gagari E, Adam RM, Damoulis PD, Freeman MR. J Dent Res. 2004 Aug;83(8):596-601. Katsumi A, Orr AW, Tzima E, Schwartz MA. J Biol Chem. 2004 Mar 26;279(13):12001-4. Epub 2004 Feb 11.

V.A.C.® Therapy™ may directly stimulate cell proliferation



Microvessel density of wounds treated with V.A.C.® Therapy™ and GranuFoam® contact was significantly higher compared to areas not covered with foam during 1st and 2nd week of treatment. Wounds treated with V.A.C.® Therapy™ and GranuFoam® had greater microvessel density compared with the same wound prior to treatment (p=0.02).

Greene AK, Ann Plast Surg. 2006 Apr;56(4):418-422.

V.A.C.® Therapy™ may directly stimulate cell proliferation

V.A.C.® Therapy™ activates key players of cell cycle regulation

Method:

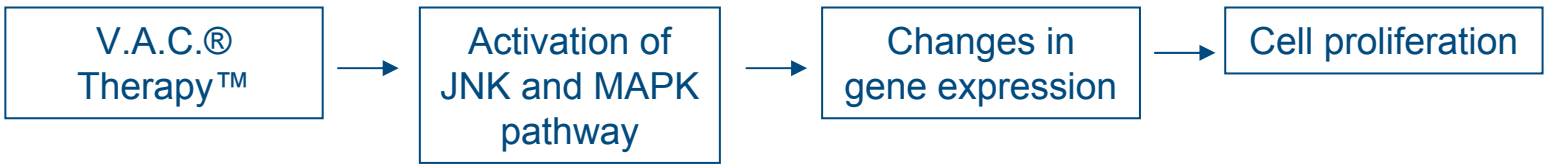
In vitro study with cultured fibroblasts
Cells were stretched (5% for 24h, 48h, and 72h) with 5 min stretch/2 min relax cycle

Result:

a) Phosphorylated **c-Jun** ↑ (at 48 and 72h of stretching)

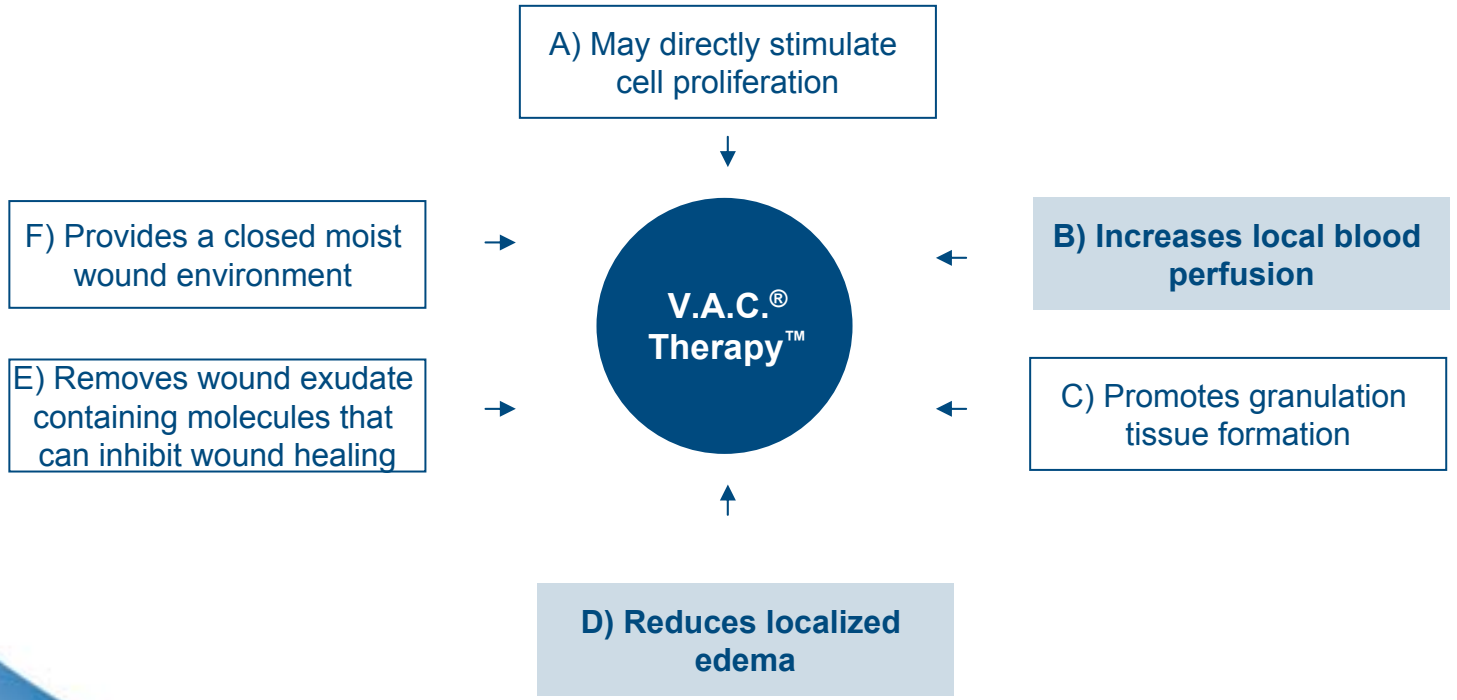
b) Phosphorylated **p38** ↑ (at 24, 48 and 72h of stretching)

c-Jun belongs to JNK signaling pathway; p38 belongs to MAPK signaling pathway

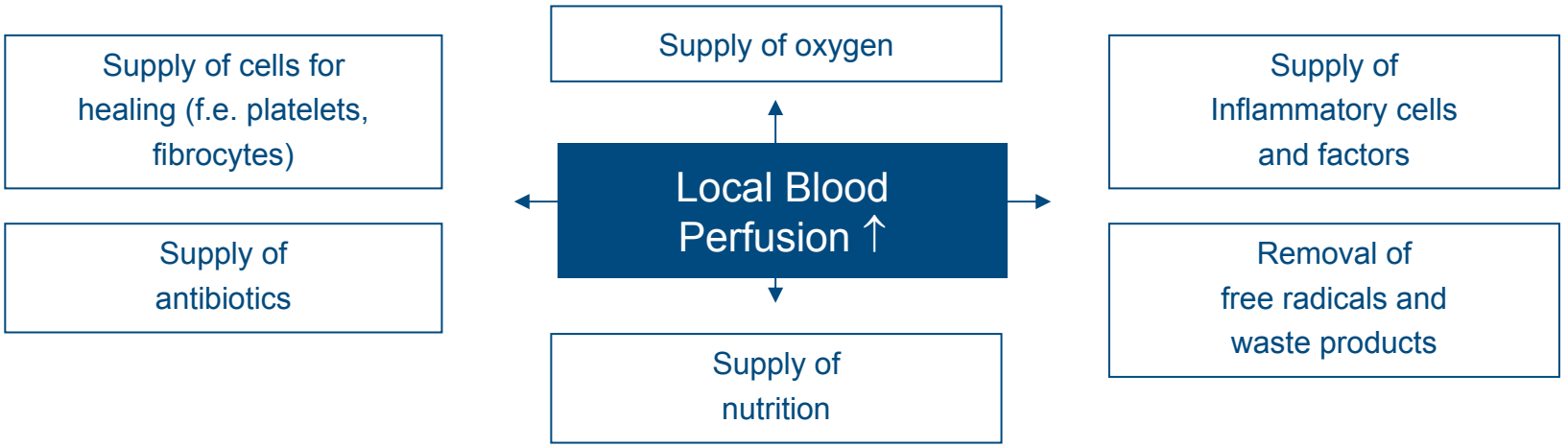


Kremers L, Kearns M, Hammon D, Scott AC, Daniel L, Morykwas MJ. Wound Repair and Regeneration, **11**(5),A3.

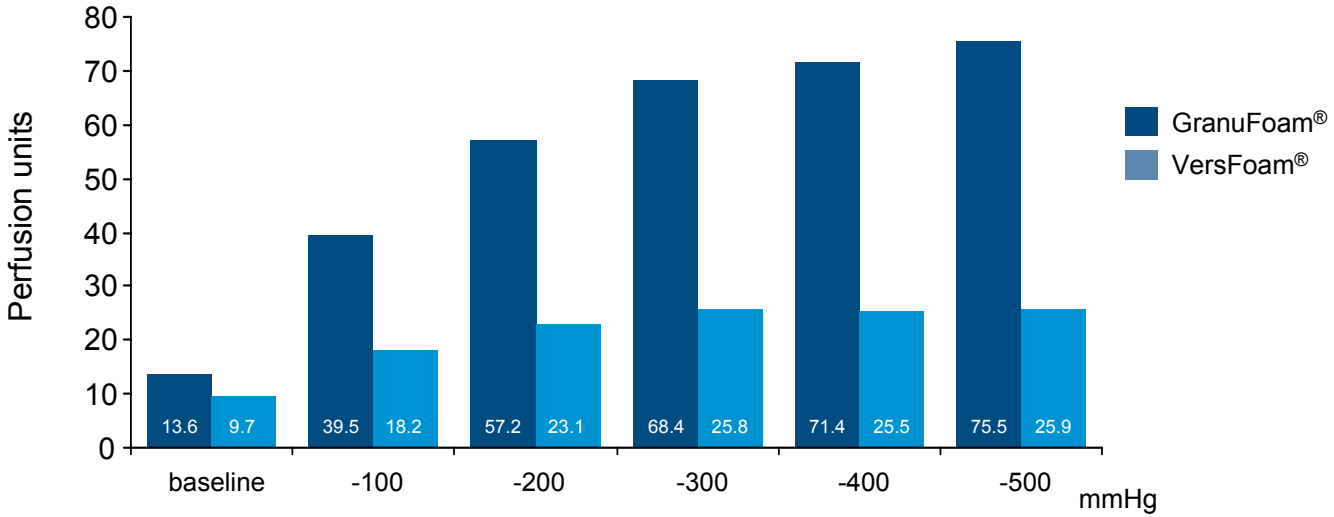
Possible mechanisms of action of V.A.C.® Therapy™



Role of local perfusion in wound healing



V.A.C.® Therapy™ increases local blood perfusion (humans/healthy skin)



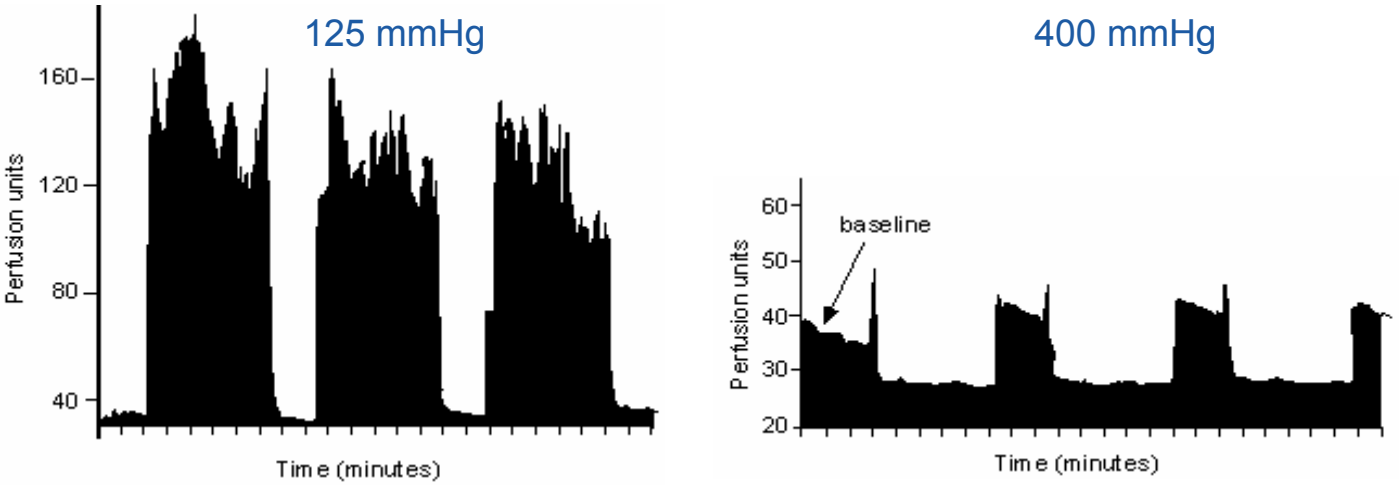
A. In intact human forearm skin mean cutaneous blood flow under the foam increases significantly when V.A.C.® Therapy™ negative pressure increases to up to -300 mmHg: $p < 0.001$

B. At –300 mmHg: over 5-fold increase in perfusion with GranuFoam® and nearly 3-fold increase with VersFoam®

C. No statistically significant increase was observed when pressure was raised above 300 mmHg

Timmers et al. Ann Plast Surg. 2005 Dec;55(6):665-71.

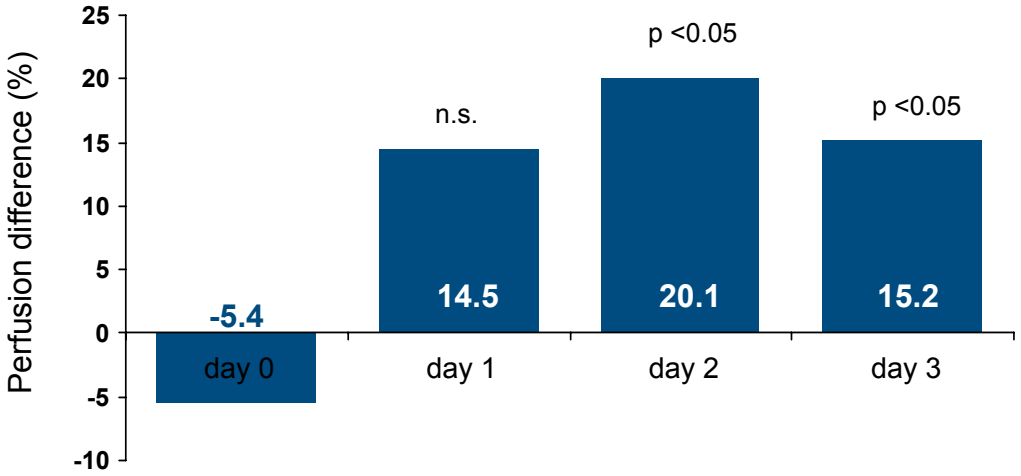
V.A.C.® Therapy™ increases local blood perfusion (animals/ wounds)



- Peak flow of four times baseline values at -125 mmHg
- Blood flow was depressed below baseline at negative pressures of -400 mmHg and above
- Intermittent application resulted in repeated increases in blood flow

Morykwas et al. Ann Plast Surg. 1997 Jun;38(6):553-62.

V.A.C.® Therapy™ increases local blood perfusion (in human burn wounds)



Seven patients with bilateral partial thickness hand burns were treated with V.A.C.® Therapy™ on the more intense injured hand and with silver sulphadiazine cream on the contra lateral one

On day 2 and 3 perfusion was significantly better in the V.A.C.® Therapy™ treated hand (resp. 20.1% (p = 0.001) and 15.2 % (p = 0.006). Oedema was reduced in the V.A.C.® Therapy™ treated hand

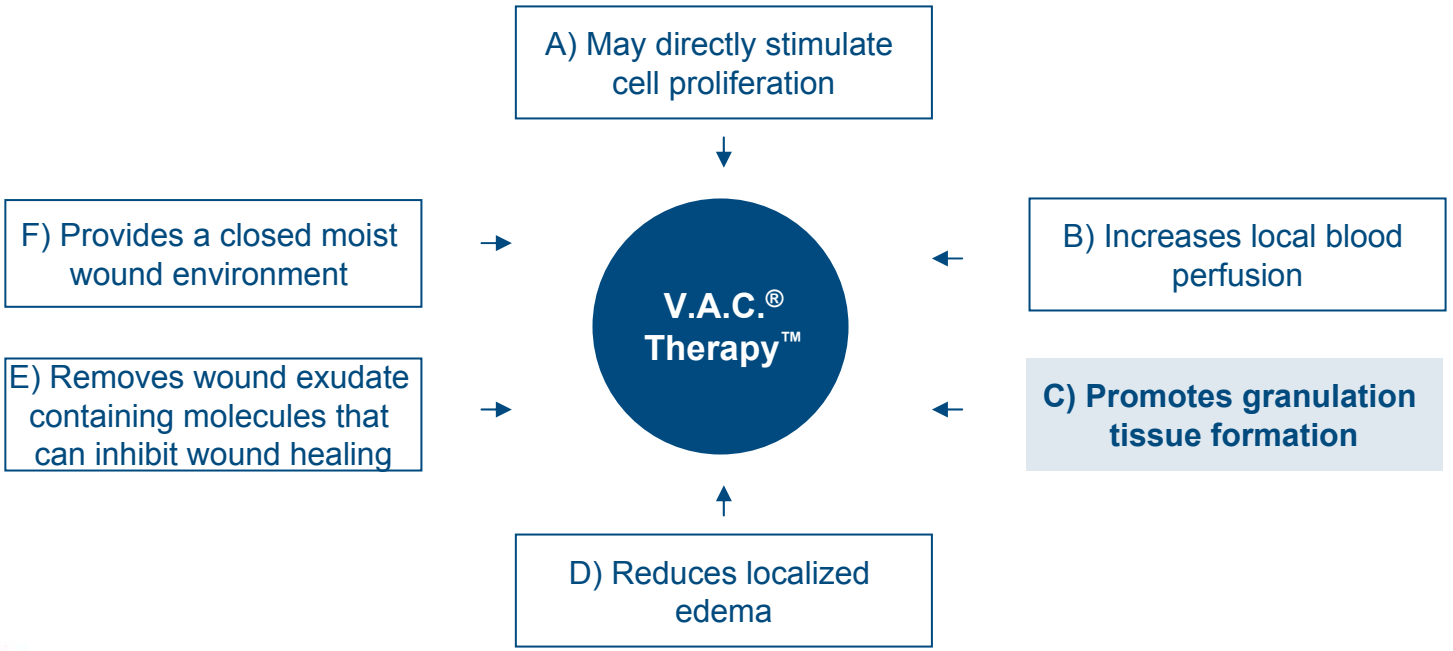
Kamolz et al. Burns 2004 (30):253-58.

V.A.C.® Therapy™ reduces localized edema

- Edema reduction in hand burns
- Massive reduction of edema in the V.A.C.® Therapy™ group (picture left hand)
- Very large amount of fluid (up to 500 ml) was removed with V.A.C.® Therapy™
- Potential Mechanisms: *Mechanical removal of fluid and effects on the inflammatory response that causes edema*
- Clinical Effect: *Reduced tissue pressure and improved capillary blood flow*

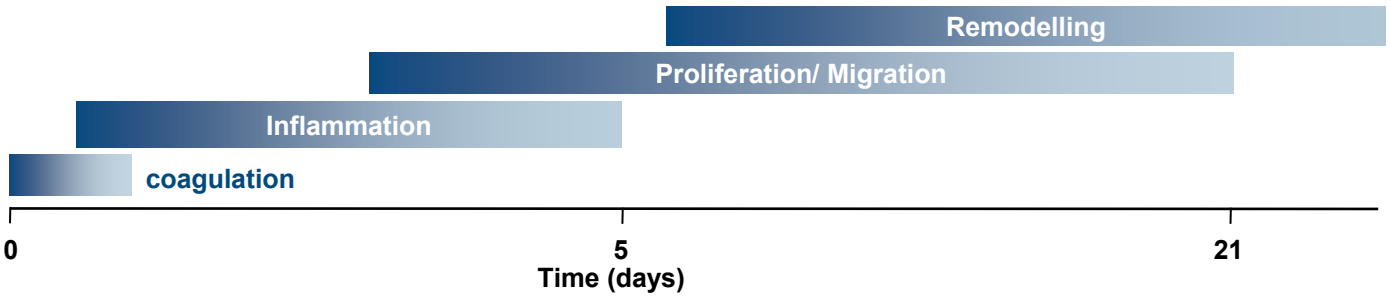
Kamolz LP et al., Burns. 2004 May;30(3):253-8.

Possible mechanisms of action of V.A.C.® Therapy™



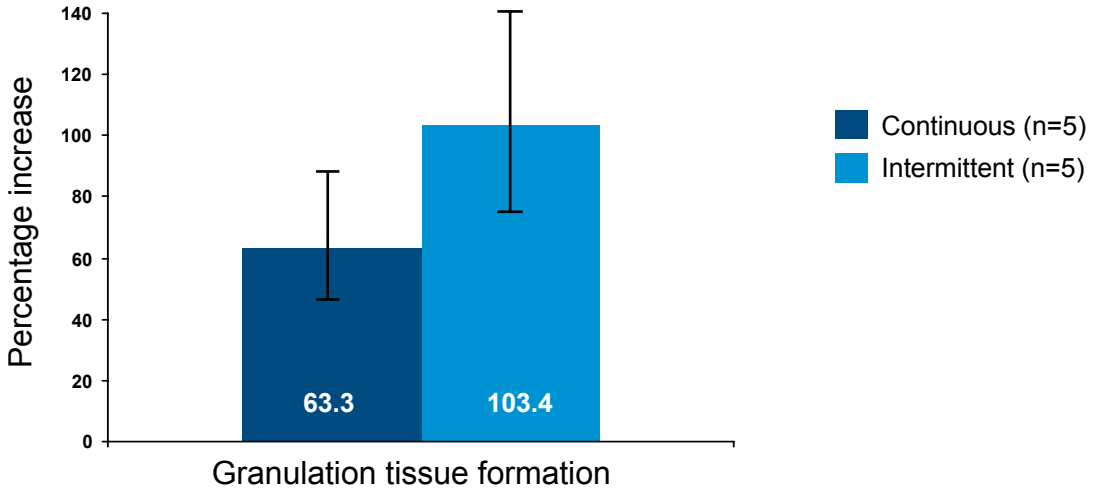
Role of granulation tissue formation in wound healing

- The formation of granulation tissue in an open wound allows the re-epithelialization phase to take place, as epithelial cells migrate across the new tissue to form a barrier between the wound and the environment.
- Granulation tissue is thus needed to fill the void that has been left by a large, open wound that crosses the basal membrane.
- Absence of granulation tissue is a feature of a non-healing wound.



Reviewed by Romo and McLaughlin, http://www.emedicine.com/ent/topic13.htm 2003. Lazarus et al., Arch Dermatol 1994;130:489-93.

V.A.C.® Therapy™ promotes granulation tissue formation

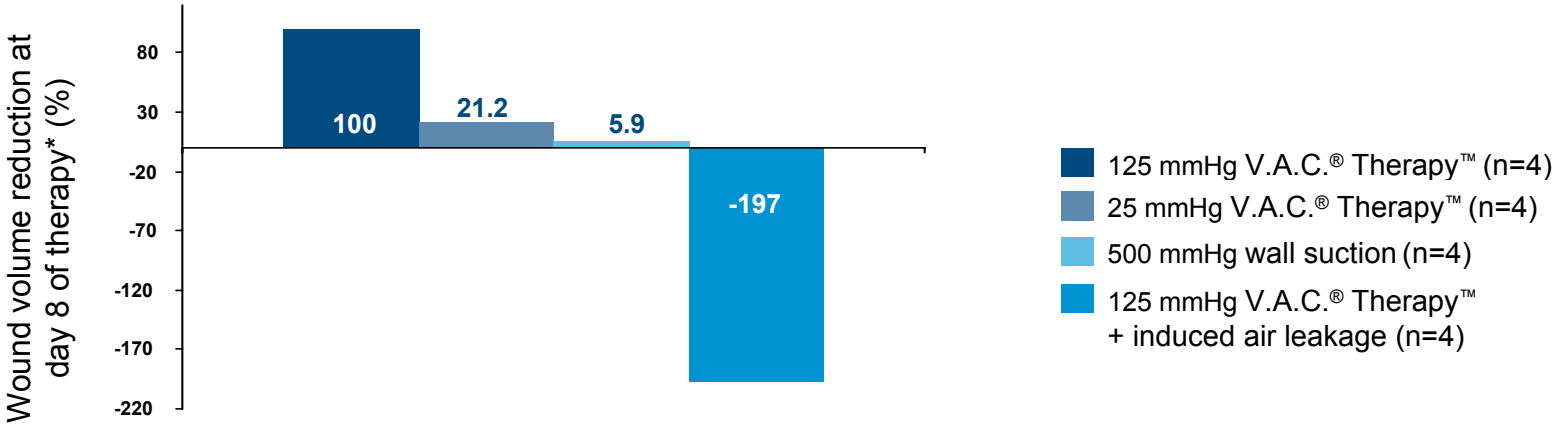


A. V.A.C.® Therapy™ treated wounds filled with granulation tissue at a significantly greater rate than control wounds (with both continuous and intermittent therapy), $p \leq 0.01$

B. The mean increase with continuous negative pressure (125 mmHg) was 63.3%, the mean increase for intermittently treated wounds was 103.4%

Morykwas et al. Ann Plast Surg. 1997 Jun;38(6):553-62.

V.A.C.® Therapy™ promotes granulation tissue formation



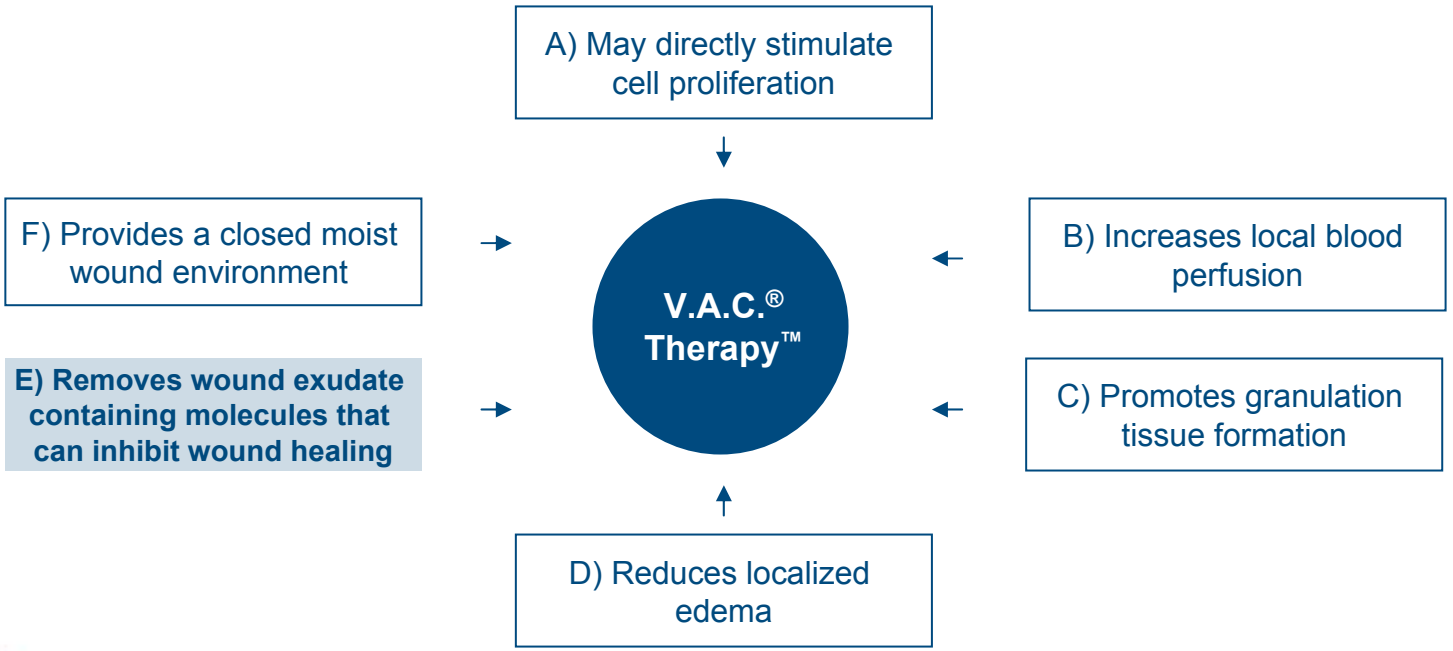
Highest wound volume reduction and rate of granulation tissue formation in wounds treated with standard recommended negative pressure of -125 mmHg. Wounds treated with V.A.C.® Therapy™ (-125 mmHg) filled with a significant higher rate than wounds treated with low (-25 mmHg) or high (-500 mmHg) negative pressure ($p<0.0001$)

Unregulated air leakage leads to wound volume increase and is a serious risk

*Wounds were treated until one of the wounds has granulated to a level flush with the surrounding tissue. Wounds treated with 125mm Hg had filled 1st completely with granulation tissue (by day 8).

Morykwas et al. Ann Plast Surg. 2001 Nov;47(5):547-51.

Possible mechanisms of action of V.A.C.® Therapy™



V.A.C.® Therapy™ removes wound exudate containing molecules that can inhibit wound healing

The Role of Matrix Metalloproteinases in Wound Healing

- Degradation of all major components of extracellular matrix
- Important for normal wound healing (e.g. removal of damaged tissue cell migration)
- MMP family
  - *Collagenases (MMP-1, MMP-8)*
  - *Gelatinases (MMP-2, MMP-9)*
  - *Strong collagenase and gelatinase (MMP-13)*

Higher levels in chronic wound fluid (versus acute wounds)

↓

Degradation of key molecules for wound healing

The Role of proinflammatory Cytokines in Wound Healing

- Non-antibody proteins released by one cell population (contact with specific antigen)
- Intercellular mediators for e.g. immune response
- TNF-α is an important and well investigated proinflammatory cytokine

Higher levels of TNF-α in chronic wound fluid (versus acute wounds)

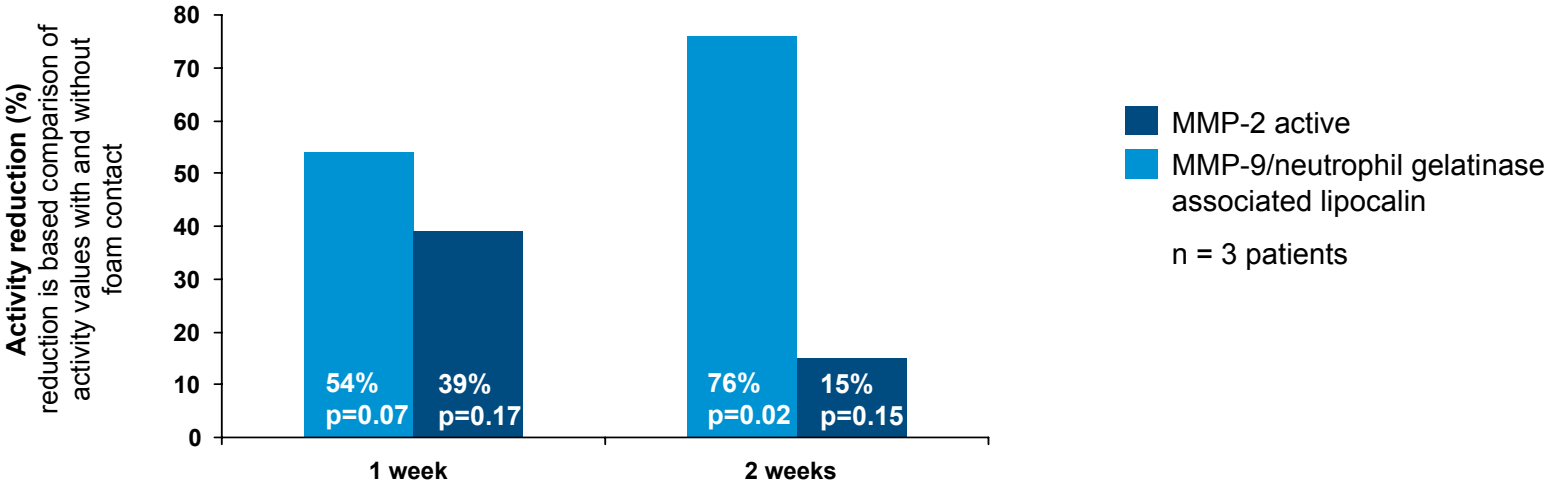
↓

- **Higher MMP activity**
- **Inhibition of Cell Cycle**

Murphy G et al. Biochem Soc Trans. 1990 Oct;18(5):812-5. Agren MS et al. J Invest Dermatol. 1992 Dec;99(6):709-14. Teot L, Banwell PE, Ziegler UE, Surgery in Wounds. Springer 2004, 30

V.A.C.® Therapy™ reduces activity of selected MMPs and inflammatory cytokines

Effect of V.A.C.® Therapy™ with and without GranuFoam® contact on MMP-2/9 activity[1]



Role of MMP-2 and MMP-9[2]

- 5-10 fold increased in chronic versus acute wound fluid
- Matrix degradation and hypothetical effect on endothelial proliferation (lowering MMP-mediated angiostatin and endostatin production)

1. Greene AK et al. Ann Plast Surg. 2006 Apr;56(4):418-422 2. Wysocki AB et al. J Invest Dermatol. 1993 Jul;101(1):64-8.

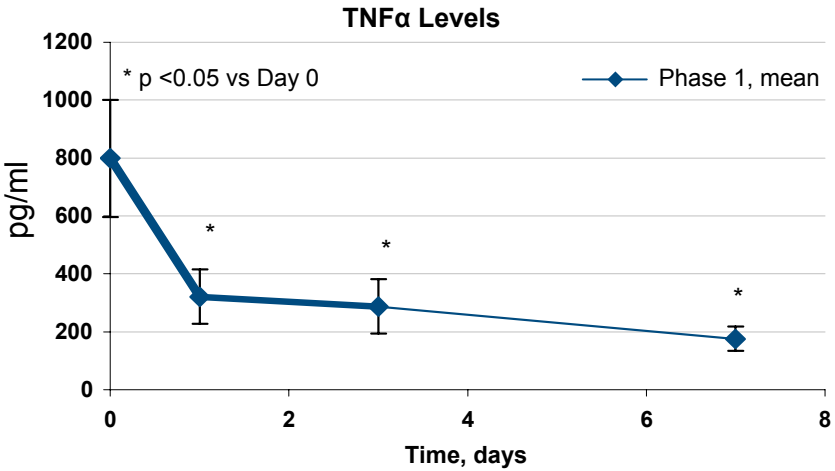
V.A.C.® Therapy™ reduces activity of selected MMPs and inflammatory cytokines

Effect of V.A.C.® Therapy™ on the Expression of MMP-1, MMP-2 and MMP13 in Human Granulation wounds

- Clinical study with n = 5 patients (chronic wounds)
- MMP-1/2/13 expression decreased following V.A.C.® Therapy™ treatment (1 week after treatment start)
- MMP-13 showed most significant decrease ($p<0.05$), mRNA levels were reduced to 1/10 at day 4 and 7

Shi B et al. Zhonghua Zheng Xing Wai Ke Za Zhi. 2003 Jul;19(4):279-81

V.A.C.® Therapy™ reduces activity of selected MMPs and inflammatory cytokines

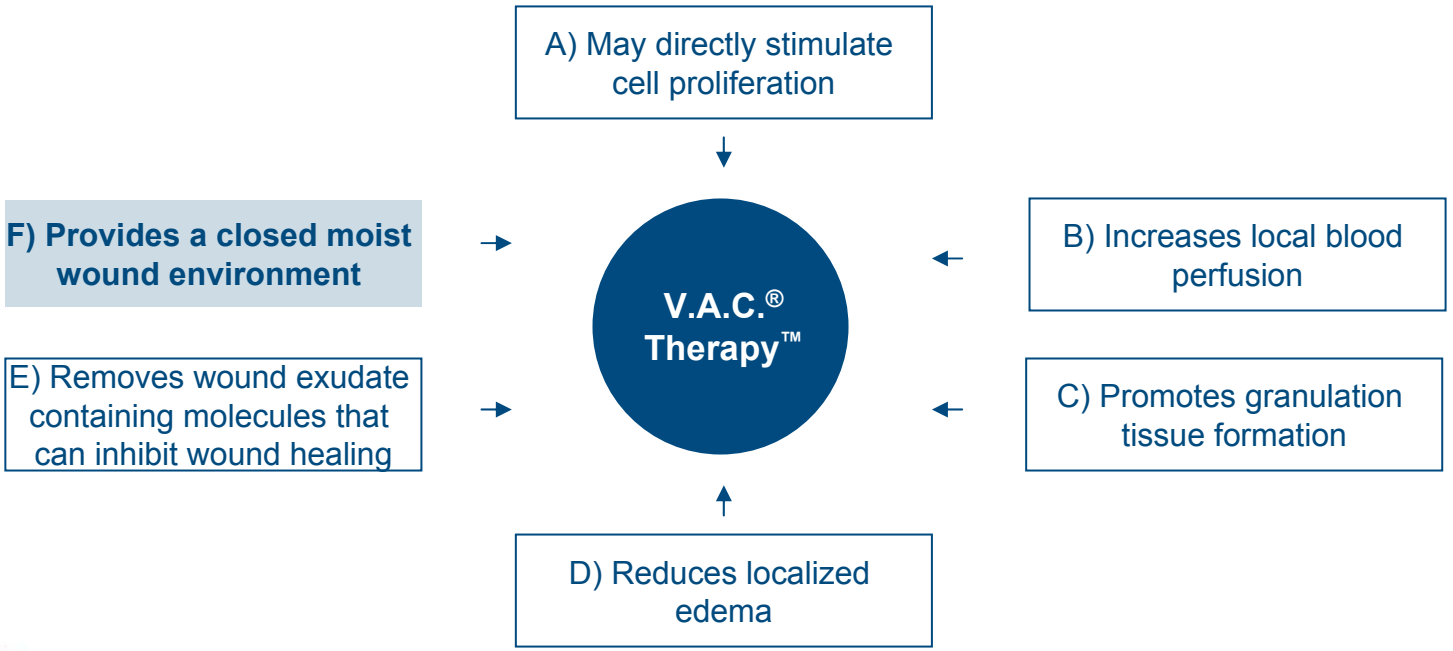


V.A.C.® Therapy™ Reduces TNFα and local Inflammation[1]

- **Goal:** Determine if V.A.C.® Therapy™ has an effect on inflammatory cytokines, proteases and protease inhibitors
- **Result:** Hospitalized pressure ulcer patients (n=8) have a significant decrease in tumor necrosis factor-alpha (TNFα) following application of V.A.C.® Therapy™

1. Stechmiller et al., to be published in May – June, 2006, *Wound Repair & Regeneration*

Possible mechanisms of action of V.A.C.® Therapy™



V.A.C.® Therapy™ provides a closed moist wound environment

- Generally accepted that moist wound environment supports healing
- Adhesive semi-occlusive drape retains moisture and allows gas exchange
- Prevents tissue dehydration
- Prevents cell death
- Adhesive semi-occlusive drape protects wound and reduces the chance of wound contamination

Summary

- Framework of basic mechanisms is supported by a theoretical model and experimental evidence
- V.A.C.® Therapy™ supports wound healing by several basic mechanisms
- Different mechanisms of action are interrelated and can act synergistically
- Major clinical effects (faster wound healing) can be explained by the evidence-based framework of basic mechanisms

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