Hot Topics in Wound Care 2011

Thomas E. Serena MD FACS FACHM MAPWCA

Founder & Medical Director - Penn North Centers for Advanced Wound Care
Chief Medical Officer - SerenaGroup
Scientific Director - New Bridge Medical Research
Vice President - American College of Hyperbaric Medicine
CEO - SERENA GROUP

Outline

• A Novel Pharmaceutical that blocks Gap junctions and controls Intercellular Communication
• Diagnostics: A tectonic shift in wound care
• A Designer matrix: growth factors and extracellular scaffold.

Current Practice

• Insert video
Developing a point of care wound diagnostic

Traditional pathway for Diagnostics (e.g. HbA1c, Creatinine, CRP):
- Proove science behind test*
- Develop validated laboratory test
- Develop validated point of care test

Systagenix development of point of care test for elevated protease activity:
- Proove science behind test*
- Develop validated point of care test

* Clinical range, levels associated with condition of interest (e.g. Kidney damage, lack of glycaemic control, infection, stalled wound healing)

Proteases in Chronic Wounds

Proteases are in excess in chronic wounds

Inflammatory Proteases Predominate

MMP level (ng/ml/mg)
- MMP-9
- MMP-8
- MMP-3
- MMP-2
- MMP-1

Vasculitis
Can you predict the level of proteases based on clinical examination?

Positive or Negative

• 63 yr old with a Venous Leg ulcer of 6 months duration. Low level of exudate.
Clinical Range

Total Inflammatory Protease Activity (184 clinical samples)

Activity Levels associated with stalled wound healing

Total Inflammatory Protease Activity (21 DFU, PU, VLU samples)

Point of Care Diagnostics
Biofilm

New gel could heal wounds 5 times faster

LONDON (AP) — For three years, Connie McPherson had debilitating leg ulcers that were so painful she sometimes ....,
Connexins and the formation of Gap Junctions

Connexin Distribution in the Skin

Immunohistochemistry Cx43 (skin): normal

Arrow is wound edge; Cx43 is green-speckled fluorescence
Bright lines in rat are auto-fluorescence of keratin
Connexin 43 in Normal Wound Healing (Skin)

After wounding:
- Decreased Cx43 expression in the cells on the margin of the wound within hours.
- Up-regulation of Cx43 in vessels near wounds

“Bystander Death and Lesion Spread”
- Gap junctions also send signals to each other and ECM
- Some of these are “death signals” (e.g., calcium)
- Dying cells can induce apoptosis in neighboring cells.
- Mediated by gap junctions including Cx43
- Cell death is directly proportion to the number and density of gap junctions within the dying cells
- This can result in “bystander cell death” and “lesion spread”


Is Connexin 43 a Potential Target for Accelerated Healing of Chronic Wounds?
Nexagon®

- NEXAGON® is
  - A selective inhibitor of Cx43 expression
  - An unmodified antisense DNA oligonucleotide that binds to the Cx43 mRNA
- Binding leads to destruction of the mRNA and thereby transient down-regulation of the protein in cells until antisense is destroyed
- The effect on Cx43 is temporary depending on delivery method (<48hrs)

Wound healing using Cx43 Antisense gel

- 6hr 1day 2day 7day
- Neonatal mice
- Incisional wound
- Cx43 ASN gel applied after wounding
- Similar findings in adult mice


Connexin 43 and Chronic Wound Healing
Human Clinical Studies

Cx43 INTACT SKIN & VENOUS LEG ULCER LOW POWER

Intact skin
Venous Leg Ulcer

Epidermis
1.4 - 6 fold increase in Cx43

Dermis
41 fold increase in Cx43

Intact skin Wound edge 4mm from edge
Initial Biopsy Conclusions

- Connexin 43 increased in wound edge of the 4 different chronic wound etiologies examined so far:
  - Venous, diabetic, vasculitic and pressure ulcers
- Connexin 43 grossly increased in epidermis compared to normal skin
  - More thickened epidermis expressing Cx43
  - More Cx43 per cell
- Connexin 43 grossly increased in dermis

*Manuscript in progress*
NOVEL Trial

- Phase IIa
- Indication: Chronic venous leg ulcers
- 4-Week, three arm trial: Vehicle, low-dose and high-dose anti-connexon (Nexagon®) (1:1:1)
- Endpoints: Safety; Surface Area Reduction; Percent Wounds Fully Closed over four weeks
- 98 patients randomized in New Zealand and USA

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<tr>
<th>Percent Complete Healers*</th>
<th>Percentage Surface Area Reduction**</th>
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<tr>
<td>100 µM</td>
<td>Per Protocol Intent-to-Treat Per Protocol Intent-to-Treat</td>
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<tr>
<td>31%</td>
<td>28% - 69% - 68%</td>
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<tr>
<td>30 µM</td>
<td>17% 18% - 61% - 59%</td>
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<tr>
<td>0 µM</td>
<td>6% 6% - 59% - 58%</td>
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<tr>
<td>100 µM vs. Vehicle</td>
<td>p = 0.017 p = 0.023 p = 0.16 p = 0.18</td>
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<td>PP Population (With and Without Erie)</td>
<td>Percent Complete Healers at 4 Weeks</td>
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Sheep- New Zealand.
Equine Pericardium-DFU Trial.
Porcine.
Synthetic- DFU

"Why can’t we put cells or growth factors in these matrix products”

Designer Scaffolds
Vitronectin-insulin growth factor complex

- Vitronectin (VN) improves the delivery of growth stimulating insulin-like growth factors (IGFs) to their receptors, type-1 IGF receptors on cell surfaces.
- The complex promotes healing by replacing the damaged extracellular matrix.