What is New in Burn Care?

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Professor of Surgery
Outline

1. Superficial burns
   - Biobrane
   - Research focus #1
2. Large TBSA burns
   - Integra versus cadaver skin
   - Epicel
3. Burn survival statistics
4. Stratagraft skin substitute
   - Research focus #2
5. Genetic engineering of Stratagraft
Superficial burns

- Clean and moist
  - Bacitracin or biologic dressing (Biobrane)
- Heal in 2 to 3 weeks
- Encourage ROM
- Pain control
The problem with silvadene
Burns are painful
Biologic dressing: Biobrane
BIOBRANE®

- Nylon Fibers
- Collagen Peptides
- Silicone Sheeting

- Nylon fabric, trifilament thread with chemically bound collagen
- Silicone outer membrane
Biobrane clinical use

Advantages
• Excellent adherence to a superficial burn
• Decreases pain
• Easy to store with long shelf life
• Relative inexpensive

Disadvantages
• Difficult to remove if left in place over 2 weeks
• Infection in 15% requires removal
• >50% infection if placed on deep dermal burns
• Therefore limited to clean superficial burns only
Research Focus #1

Functionalization of Biobrane® using Silver-Nanoparticle Polymer Films

IM-BED Biosciences
Advanced materials for wound healing
Assembly of polymeric thin films of silver nanoparticles

PAH, pK$_a$ ~ 9
poly(allylamine hydrochloride)

PAA, pK$_a$ ~ 5
poly(acrylic acid)

< 100 nm
Add AgNO$_3$

More Ag$^+$ can be added to regenerated -COO$^-$

Reducing agent

-Reduces Ag$^+$ to Ag$^0$
-Regenerates -COO$^-$

Ag NPs
Mechanical transfer of films onto Biobrane®

A

Polymer Film with
Silver
Nanoparticles

Elastomeric
stamp

Nylon Fibers

Collagen Peptides

Silicone Sheeting

Biobrane®

B

Stamp removed

Silver Loaded Polymer Film

Figures Not to Scale
Modified Biobrane® provides sustained release of silver ions

Modified Biobrane® release less than 1 µg/cm² of Ag⁺ per day in milliQ water

Comparison: Silver dressing Acticoat® release ~100 µg/cm² of Ag⁺ per day*
Silver-nanoparticle polymer film on Biobrane® causes $6\log_{10}$ reduction in bacterial counts in vitro.

![Graph showing bacterial counts over time for different materials and conditions.]

Similar response against *Staph. aureus* and *Pseud. aeruginosa*.
Splinted-wound-infection model

- Heterozygous wild mice
- Full-thickness cranial wounds (6 mm diameter) splinted
- Wounds inoculated with *Staph. aureus* and covered with Biobrane®
- Secured with Tegaderm
- Wounds harvested on day 3 and homogenized for bacterial counts
Biobrane® modified with silver-nanoparticle films prevents infection in full-thickness mice wounds

• Heterozygous wild mice
• Wounds inoculated with $3 \times 10^4$ CFU on day 1
• Wounds harvested on day 4

$n=12$ wounds
$p<0.01$, t-test

Similar response against *Staph. aureus*
Biobrane® modified with silver-nanoparticle films reduces bacteria in partial-thickness pig wounds

- Wounds inoculated with $3 \times 10^6$ CFU on Day 0
- Control wounds treated with unmodified Biobrane®
- Wounds harvested at day 3

Statistically significant difference ($p < 0.001$)

$n=12$ wounds

Similar response against *Staph. aureus*
Conclusions

• Biobrane® integrated with silver-nanoparticle films significantly reduced bacterial growth in vitro and in skin wounds in mice and pigs

• Future directions
  – Other antibacterial agents (silver nanoparticles, chlorhexidine)
  – Growth factors
  – Integra
  – Biologics used for abdominal wall reconstruction

• In discussion with UDL to obtain IND
  – Avoid Biobrane associated infection
  – Expand indication for use to deeper dermal burns
Large TBSA burns
<20% of burns are large TBSA
Burn shock correlates with TBSA

- Loss of vascular integrity
- Increased metabolic rate
- Catabolic - futile substrate cycling
- Depressed immune function
- Cardiac depression
- Shortened RBC life
- Renal and MSOF
Resuscitation with Parkland formula

- $4 \times (\% \text{TBSA}) \times (\text{kg body weight})$
- total fluid needs for first 24 hours
- 1/2 vol. during first 8 hours
- 1/2 vol. during next 16 hours
Burn resuscitation

Resuscitation vol. (ml/kg/%burn/hr) vs Time post-burn (hours)

Calculated volume requirements (4 ml/kg/%burn)
Other controversies in resuscitation

- Use of colloid
- Hypertonic saline
- FFP as resuscitation fluid
- Vitamin C, zinc and other adjuncts
Early excision to prevent burn wound sepsis
Meshed skin greatly expands coverage
What to do if there is inadequate donor site available?

Weekly application of allograft
  OR
Integra
  Then
Serial harvesting of available donor sites (?)epicel)
Integra technique
Integra technique
Integra versus allograft

• Allograft
  – Theoretic infection risks
  – Must be replaced weekly, multiple operations
  – Inexpensive and available

• Integra
  – Expensive
  – 3 weeks to revascularization
  – Prone to infection
  – Able to use thin and widely meshed autografts
  – May improve cosmesis
  – May improve function
Epicel - cultured epidermal autografts

- Cultured keratinocytes - 1983
- 2-8 cell layers thick
- Neodermal formation after one year
- Two 6 X 2 cm skin biopsies
- 15 day lag time
Cultured epidermal autografts

• Advantages
  – limitless supply
  – save available donor for hands, face

• Disadvantages
  – $825 per graft (petri dish, 50 cm²)
  – keratinocyte replacement only
  – 50% success rate
Epicel
The art of burn surgery

- Timing of excision
- Timing of first STSG
- Treatment of hands and faces
- Coverage of large open areas
- Donor site utilization
- 4th degree burns with exposed tendon/bone
- Life/Function/Cosmesis
Outcomes
## Mortality versus TBSA

<table>
<thead>
<tr>
<th>%TBSA</th>
<th>Lived No. of Cases</th>
<th>Died No. of Cases</th>
<th>Mortality Rate</th>
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</thead>
<tbody>
<tr>
<td>0.1 - 9.9</td>
<td>62,113</td>
<td>403</td>
<td>0.6</td>
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<tr>
<td>10 - 19.9</td>
<td>17,064</td>
<td>518</td>
<td>2.9</td>
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<tr>
<td>20 - 29.9</td>
<td>5,267</td>
<td>473</td>
<td>8.2</td>
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<tr>
<td>30 - 39.9</td>
<td>2,277</td>
<td>419</td>
<td>15.5</td>
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<td>40 - 49.9</td>
<td>1,093</td>
<td>352</td>
<td>24.4</td>
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<td>596</td>
<td>336</td>
<td>36.1</td>
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<td>60 - 69.9</td>
<td>398</td>
<td>297</td>
<td>42.7</td>
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<td>70 - 79.9</td>
<td>215</td>
<td>289</td>
<td>57.3</td>
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<tr>
<td>80 - 89.9</td>
<td>128</td>
<td>286</td>
<td>69.1</td>
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<tr>
<td>&gt; 90</td>
<td>97</td>
<td>397</td>
<td>80.4</td>
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<tr>
<td><strong>Subtotal</strong></td>
<td><strong>89,248</strong></td>
<td><strong>3,770</strong></td>
<td><strong>4.1</strong></td>
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<tr>
<td><strong>Missing or 0%</strong></td>
<td><strong>32,737</strong></td>
<td><strong>1,261</strong></td>
<td><strong>3.7</strong></td>
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<tr>
<td><strong>TOTAL</strong></td>
<td><strong>121,985</strong></td>
<td><strong>5,031</strong></td>
<td><strong>4.0</strong></td>
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</tbody>
</table>

Total N = 127,016
Mortality by Baux score

- Burn Size
- Age
- Inhalation Injury

Baux score = Age + % TBSA
Estimated Baux30 = 108.9

Age + % TBSA

2
Rapid decline in mortality over time

Dashed lines are approximate 95% confidence limits
# Mortality by age group - decreased

<table>
<thead>
<tr>
<th>Age</th>
<th>0–14</th>
<th>15–44</th>
<th>45–64</th>
<th>&gt;65</th>
<th>All</th>
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<tr>
<td>1980s</td>
<td>1.2</td>
<td>6.1</td>
<td>18.7</td>
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<td>1990s</td>
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<td>3.4</td>
<td>5.5</td>
<td>20</td>
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<td>2000s</td>
<td>0.2</td>
<td>1.8</td>
<td>5.1</td>
<td>17.7</td>
<td>2.3</td>
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</table>
LA50 has increased

<table>
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<th></th>
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<tbody>
<tr>
<td>0–14</td>
<td>55.3</td>
<td>74.3</td>
<td>100</td>
</tr>
<tr>
<td>15–44</td>
<td>55.7</td>
<td>49.6</td>
<td>76.4</td>
</tr>
<tr>
<td>45–64</td>
<td>32.6</td>
<td>50.9</td>
<td>58.6</td>
</tr>
<tr>
<td>&gt;65</td>
<td>13.6</td>
<td>28.1</td>
<td>27.8</td>
</tr>
</tbody>
</table>
Research focus #2
The unique problem of deep partial thickness burns

- Will heal without STSG
- But, scarring can be significant
- Lack of donor site availability in those with large TBSA burns
Allogeneic keratinocytes improve healing of deep dermal burns

• Rab et al, Burns 2005: Should dermal scald burns in children be covered with autologous skin grafts or with allogeneic cultivated keratinocytes
Allogeneic keratinocytes improve healing of deep dermal burns
Cultured skin substitutes in deep dermal burns

- Living tissue interacts with the wound bed
- Immediate wound coverage
- Barrier function
- Controls pain
- Allogeneic cells are replaced with autologous keratinocytes by 3 months
- There is no consistent source of allogeneic keratinocytes with full barrier function
Stratagraft core technology

NIKS® cells
- Proprietary human epidermal progenitors
- FDA CMC testing complete
- Multiple cell banks in place

Epidermal layer:
NIKS® cells
+ Dermal layer:
human fibroblasts
and collagen

Cultured under proprietary conditions

Fully developed multi-layered human skin
- Physical barrier present
- Biologically active
- Strong, durable, suturable

StrataGraft®
Phase I clinical trial

- **NIH/NIAMS R44-AR47499 Translational Clinical Grant**

- Full-thickness wounds ≥5% TBSA requiring serial debridement and grafting

- Temporary coverage for 7 days with StrataGraft® and cadaver allograft

- Primary efficacy outcome was autograft take at 2 weeks
Phase I clinical trial results

Cadaver allograft, day 7

StrataGraft®, day 7

Cadaver allograft, 2 weeks post STSG

StrataGraft®, 2 weeks post STSG
Phase IIb clinical trial

- Stratagraft can be used as a temporary wound cover in patients with deep dermal burns after operative debridement
  - Clinical trial grant funded by DOD (AFIRM)
  - Randomized trial of Stratagraft versus STSG
  - Multicenter trial 7/20 patients
  - First patient enrolled at UCH
  - 100% success in first 7
Genetic engineering of Stratagraft

• Expressgraft
  – Bacterial bioburden
  – Poor vascular ingrowth
  – Abnormal proteases
- **Defensins**
  - $\alpha$, $\beta$: most prevalent in epithelial tissues
- **Cathelicidin** - keratinocytes, neutrophils, and mast cells
  - Antimicrobial
  - Chemotactic
  - Angiogenic
  - Work in synergy with other HDP

NIKS$^{hBD-3}$

NIKS$^{hCAP-18}$
Stable tissue-specific expression of hCAP-18 mRNA
Murine burn infection model provides method for \textit{in vivo} assessment of NIKS$^{hBD-3}$ tissue.

24 hr

72 hr after skin grafting:
Quantitative culture of skin tissue and underlying muscle
NIKS^{hCAP-18} tissues inhibit growth of acinetobacter in a burn infection model.
NIKS\textsuperscript{hCAP-18}

- Approved by the RAC committee at NIH
- IND at FDA
- DFU trial funding from NIH
- Early 2013
VEGF protein levels expressed by pro-angiogenic NIKS clones:

* P < 0.005
Visualizing FITC-stained vessels within the CMA

(-) Media Control

(+) bFGF Control

NIKS\textsuperscript{HIF-1$\alpha\Delta$ODD}

NIKS\textsuperscript{VEGF-165}