Burn Repair with Engineered Skin Substitutes

Steven Boyce PhD, David Greenhalgh MD
Tina Palmieri M D, Petra Warner MD
Kevin Yakuboff MD, Kevin Bailey MD, David Herndon MD,
Peggy Simpson RN, and Richard Kagan MD

Dept of Surgery, University of Cincinnati
Shriners Hospitals for Children
Cincinnati, OH, Sacramento, CA and Galveston, TX
Medical Objectives

- Survival
- Earliest closure
- Least donor skin
- Minimum scar
  - Acute burns
  - Burn scars
  - Congenital lesions
  - Chronic wounds

Boyce, NJBS 2008
Human Skin: Structures & Functions

- **Three B’s:**
  - **Barrier**
  - **Basement membrane**
  - **Blood supply**
Skin Biopsy

Isolate & Culture Cells

Biopolymer Substrate

Cultured Skin Substitute

Boyce, NJBS 2008
TIMELINE TO WOUND CLOSURE

- Earlier closure → Less risk (sepsis/scarring)
- Fewer surgeries → Less stress
- Shorter ICU & Wounds Closed

% TBSA FT Burn

Months

- Shorter ICU
- ICU

Boyce, NJBS 2008
Selective Culture of Skin Cells

Fibroblasts

Keratinocytes

DMV Endothelial Cells

Melanocytes

Boyce, NJBS 2008
Engineered Skin Substitute

• biopolymer (collagen sponge)
• partially stratified epithelium (e) attached to a dermal substitute (d), avascular, no appendages, 0.3-0.5 mm thick
• ~ 30 or 120 cm² in area

Boyce, NJBS 2008
Measure of Epidermal Barrier for QA

Dermal-Epidermal Junction in ESS

AG

ESS

BrdU

Col IV

LAM 5

Integin β4

Boyce, NJBS 2008
Melanocytes in ESS: 5 weeks

Boyce, NJBS 2008
Preclinical Projects with ESS

- Matching of skin color (melanocytes)
- Automation of manufacturing (bioreactors)
- Electro-spinning of biopolymers
- Vascularized device (endothelial cells)
- Suppression of scarring (fetal healing)
- Extended lifespan & adnexi (stem cells)
## Patient Demographics

$n = 54$ patients; 1998-2005

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SEM</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>7.6 ± 0.7</td>
<td>0.6 – 18</td>
</tr>
<tr>
<td>Gender ratio (M / F)</td>
<td>(38 / 16)</td>
<td>n.a.</td>
</tr>
<tr>
<td>% TBSA burn</td>
<td>73.9 ± 1.6</td>
<td>53 - 95%</td>
</tr>
<tr>
<td>% TBSA FT burn</td>
<td>70.3 ± 2.2</td>
<td>32 - 95%</td>
</tr>
<tr>
<td>% TBSA CSS / pt</td>
<td>26.5 ± 2.7</td>
<td>5 - 88%</td>
</tr>
<tr>
<td>Days to 1&lt;sup&gt;st&lt;/sup&gt; CSS</td>
<td>34.8 ± 1.0</td>
<td>24 – 59</td>
</tr>
</tbody>
</table>

Boyce et al., J Burn Care Res, 2006; J Trauma, 2006
Surgical Methods

• **ESS were:**
  - ~ 6 X 6 cm, or 12 X 12 cm
  - covered with N-Terface™
  - attached with staples

• **Dressings were:**
  - fine mesh gauze
  - coarse gauze
  - irrigated with antimicrobials
  - stretched Spandex™
Results

POD 14

POD 28

Boyce, NJBS 2008
Results

POD 69

POD 479
Results (54 subjects)

Engraftment

% Area Closed at POD 14

- ESS: 79.5
- AG: 95.7

Closed: donor area

- ESS: 61.5, * p < 0.05
- AG: 4

Boyce, NJBS 2008
Results

TBSA closed: POD 28

- ESS
  - 19.1
  - * p<0.05
- AG
  - 50.5

TBSA covered vs % FT burn

- % TBSA Full-thickness Burn
- % TBSA Closed with CSS, POD 28

- r = 0.64
- p < 0.0001

Boyce, NJBS 2008
Results: Vancouver Score

pod range 14-27 28-62 63-182 183-364 >364

Vancouver

0 1 2 3 4 5

normal scar

* p<0.05

POD range 14-27 28-62 63-182 183-364 >364

ESS AG

Boyce, NJBS 2008
Outcome:
81% TBSA, PBD

Weeks 6 & 7
Week 9
Week 8
Week 10
Week 11
Outcome after 95% TBSA Burns

3-6 months after treatment

Boyce, NJBS 2008
Scar Reconstruction

EpiCel failure

ESS success

Right arm

Left arm

Boyce, NJBS 2008
Extramural Engineered Skin

<table>
<thead>
<tr>
<th>City</th>
<th># enrolled</th>
<th># treated</th>
<th># operations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sacramento</td>
<td>15</td>
<td>10</td>
<td>27</td>
</tr>
<tr>
<td>Galveston</td>
<td>14</td>
<td>7</td>
<td>33</td>
</tr>
<tr>
<td>Boston</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Edmonton</td>
<td>1</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>33</strong></td>
<td><strong>19</strong></td>
<td><strong>72</strong></td>
</tr>
</tbody>
</table>

1898 devices: 4.9 m²
Commercialization of ESS

- Technology licenses to Cutanogen Corporation
- Cutanogen acquired (2006) by Cambrex/Lonza
- Tech Transfer (cGMP manufacture)
- Regulatory filings
  - HDE being prepared
  - IDE/PMA being planned
- FDA audits pending completion

Boyce, NJBS 2008
Therapeutic Opportunities with ESS

- Reduced morbidity from burns
- Burn scar reconstruction
- Chronic wounds
- Congenital skin lesions
# Engineered Skin Collaborators

## Clinical
- Richard Kagan, MD
- Petra Warner, MD
- Kevin Yakuboff, MD
- Kevin Bailey, MD
- Peggy Simpson, RN
- Mary Rieman, RN
- Alice Neely, PhD

## Laboratory
- Chris Lloyd, BS
- Liz Maier, BS
- John Besse, BS
- Rachel Zimmerman, BS
- Jill Pruszka, BS
- Rachel Rice, BS
- Deanna Snider, BSHT

## University
- Dorothy Supp, PhD
- John Kitzmiller, MD
- Steven Hoath, MD
- Gerald Kasting, PhD
- Randy Wickett, PhD
- Zalfa Abdel-Malek, PhD
- Alice Neely, PhD

## Extramural
- David Greenhalgh, MD
- Joachim Kohn, PhD
- George Muschler, MD
- Arnold Caplan, PhD
- Heather Powell, PhD
- Adam Katz, MD
- David Herndon, MD

## Past
- Richard Ham, PhD
- John Hansbrough, MD
- Glenn Warden, MD
- Ian Alan Holder, PhD
- Mary Williams, MD
- Residents, post-docs and staff

Boyce, NJBS 2008
Project Sponsors

• Shriners Hospitals for Children
• National Institute of General Medical Sciences
• US Department of Defense
• State of Ohio Department of Development
• FDA Office of Orphan Product Development