Principles, Practices and Prospects for Burn Wound Management

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Disclosure

• ANZBA travel support provided by Skin Tissue Engineering
Burn Size Group (% TBSA) vs Number of Cases and % Mortality

National Burn Repository: 2015 Report Amer Burn Assn; n=172,550
Medical Objectives

• Survival
• Earliest closure
• Least donor skin
• Minimum scar
  • Acute burns
  • Burn scars
  • Congenital lesions
  • Chronic wounds
Human Skin: Structures & Functions

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

Skin Biopsy

Isolate & Culture Cells

Cryopreservation

Biopolymer Scaffold

Engineered Skin Substitute

10,000 cm² burn
- 4,000 cm² AG
6,000 cm² ESS
X 0.01
60 cm² biopsy
Ideal Properties of Biopolymers

- Biocompatibility (low immunogenicity)
- Proper degradation rate for indication
- Self-assembly into higher order structures
- Appropriate mechanical properties
- Cell adhesion, migration, and proliferation
- Dry storage (banking)
Acellular Polymers & Matrices: Chemical Engineering

• Non-degradable
  • metals, alloys
    • stainless steel
    • titanium alloys
  • plastics
    • PTFE
    • HDPE
    • bone/dental cements
  • ceramic/glass composites

• Degradable
  • synthetic
    • PGA/PLA (Vicryl, Dexon)
    • PCL
    • PU
  • tissue-derived
    • collagens / gelatin
    • fibrin
    • hyaluronan
    • elastin
Challenge of Degradable Polymers

Synthetics
- Simple chemically
- Pure pharmaceutically
- Very reproducible
- Biologically deficient
- May be immunoreactive
- Less biocompatible

Biologics
- Complex biochemically
- Not pure pharmaceutically
- More variable
- Biologically efficient
- Much less immunoreactive
- More biocompatible

Balance
Dermal-Epidermal Junction in ESS

Boyce et al, J Invest Dermatol 118:565-572
Major Shifts in Gene Expression of ESS ± Grafting

Klingenberg et al, JID, 2010

- 10,359 probe sets
- 11 expression clusters
- normalized to d3 in vitro
- through 8 wks in vivo
Study Objectives

Compare an autologous engineered skin substitute (ESS) to meshed and expanded, split-thickness skin autograft (AG) for burns greater than 50% TBSA.

• Randomized, paired-site comparison to determine the:
  • percentage engraftment (POD 14)
  • ratio of closed wound to biopsy area (POD 28)
  • percentage TBSA covered
  • correlation of % TBSA closed with %TBSA FT burn
  • frequencies of regrafting
  • antibody production to the biopolymer implant
Demographic Data of the Patient Population

\( n = 16 \) enrolled
15 treated, 1 expired pretreatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SEM</th>
<th>Range</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>6.3 ± 1.1</td>
<td>1.4 - 17.5</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>(14 / 2)</td>
<td>n.a.</td>
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<tr>
<td>TBSA burn (%)</td>
<td>79.1 ± 2.2</td>
<td>59.5 – 95.0%</td>
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<tr>
<td>TBSA FT burn (%)</td>
<td>77.9 ± 2.4</td>
<td>58.8 – 95.0%</td>
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<tr>
<td>TBSA ESS/subject</td>
<td>33.4 ± 3.5</td>
<td>9.7 – 71.6%</td>
</tr>
<tr>
<td>Days to first ESS</td>
<td>32.1 ± 1.1</td>
<td>24 – 42</td>
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Study was performed under an Investigative Device Exemption regulated by the US FDA.

Surgical Methods
Lower left, ESS application
Upper left, Comparative grafting
Upper right, Wet dressings
Non-cytotoxic antimicrobials
Surgical Methods: ESS and AG
2056 ESS grafts, 4.89 m², 59 operative procedures
Results: Clinical Examination POD 28, 62

POD 28

POD 62
Results: Histology, POD 105

ESS

AG
74% TBSA, FT Burn: POD 360

Upper body

Comparative sites
Results: % Mortality and % Engraftment (POD 14)

Expansion Ratio and % TBSA closed (POD28)

Results: POD28

% TBSA burn vs % TBSA closed

Frequencies of regrafting

ELISA for bovine collagen

94% TBSA FT Burn; Clinical Exam PBD 225
Recovery of Normal Activities after 94% Burns

POD 405
Conclusions & Interpretations

• Autologous ESS can reduce mortality and donor site harvesting in pediatric burns greater than 50% TBSA.

• Stable wound closure is interpreted to result from:
  • preservation of epidermal progenitor cells
  • formation \textit{in vitro} of basement membrane between fibroblasts and keratinocytes, and
  • generation of fibro-vascular tissue by the biopolymer scaffold.
Restoration of Skin Color

Clinical hypopigmentation

Engineered skin no melanocytes added

Engineered skin with melanocytes added

Swope et al, Wound Rep Regen, 2006
Melanocyte Density *In Vitro* (7-14 days)

TRP-1 staining *en face* image analysis

*Boyce et al, Pigment Cell & Melanoma Res; epub, 22 Jun 2017*
hM Retention in ESS-P *In Vivo* (12 wks)

*Media: UCMC160 vs UCDM1*

- **A** Closed Wound
- **B, E, H, K, I, L** Micro Anatomy
- **C, F, G, J** TRP1 for hM

- **No added hM**
- **Fresh hM UCMC160**
- **Frozen hM UCMC160**
- **Fresh hM UCDM1**
Grafting of ESS-P to Immunodeficient Mice

% Pigmented Area vs time; Mexameter vs time

Pigmented Area

Pigment Density

Boyce et al, Pigment Cell & Melanoma Res; epub, 22 Jun 2017
Melanocyte Density *In Vivo* (12 wks)
Mel-5 staining, *en face* image analysis

hM in Epidermis

hM Density

Summary

- Autologous ESS may offer an alternative therapy for FT burns >50% TBSA
- Natural pigment may be restored in ESS by transplantation of autologous melanocytes
- Optimized media promote increased efficiency of melanocyte transplantation
# Engineered Skin Collaborators

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- Residents, post-docs and staff

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Project Sponsors

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