Application of Bioengineered Allogeneic Construct

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StrataGraft® Is a New Investigational Biologic for the Treatment of Severe Thermal Burns That Contain Intact Dermal Elements and Require Surgical Intervention*

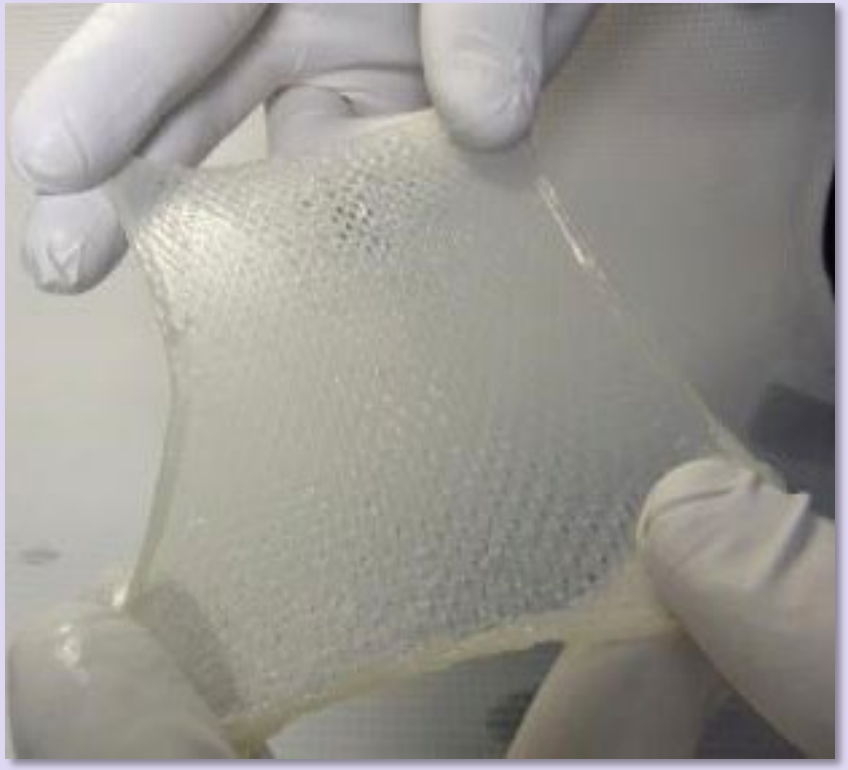
Viable, bioengineered, allogeneic cellularized scaffold product developed to reduce autograft in patients with severe thermal burns[1]

Designed with both **inner dermis-like and outer epidermis-like layers** composed of well-characterized human cells[1,2]

Stimulates the body's own ability to heal[1,3]

Granted **RMAT** designation from the FDA under the provisions of the 21st Century Cures Act—**the only RMAT-designated product for the treatment of burns**[4,5]

Cryopreserved, **readily available,** and **not patient-specific**, with a **format familiar** to burn surgeons, making it **easy to apply**[1]



FDA – U.S. Food and Drug Administration; RMAT – regenerative medicine advanced therapy
*StrataGraft is an investigational product, and its safety and effectiveness have not yet been established by the FDA.

1. StrataGraft skin construct [prescribing information]. Madison, WI: Stratatech Corp. Submitted to FDA April 2020.
2. Schurr MJ, Foster KN, Centanni JM, et al. Phase I/II clinical evaluation of StrataGraft skin tissue: a consistent, pathogen-free human skin substitute. J Trauma. 2009;66(3):866-874.
3. Harvestine J, Pradhan-Bhatt S, Steiglitz BM, Maher RJ, Comer AR, Gratz KR, Allen-Hoffmann BL. StrataGraft® Skin Tissue, a Bioengineered Regenerative Skin Construct for Severe Acute Wounds. Poster presented at 2020 Biomedical Engineering Society (BMES) Virtual Annual Meeting, October 14–17, 2020.
4. U.S. FDA designates Mallinckrodt's StrataGraft skin tissue® as Regenerative Medicine Advanced Therapy. Mallinckrodt Pharmaceuticals. http://www.mallinckrodt.com/about/news-and-media/2286957. Published July 18, 2017.
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StrataGraft Possesses Unique Characteristics[1]

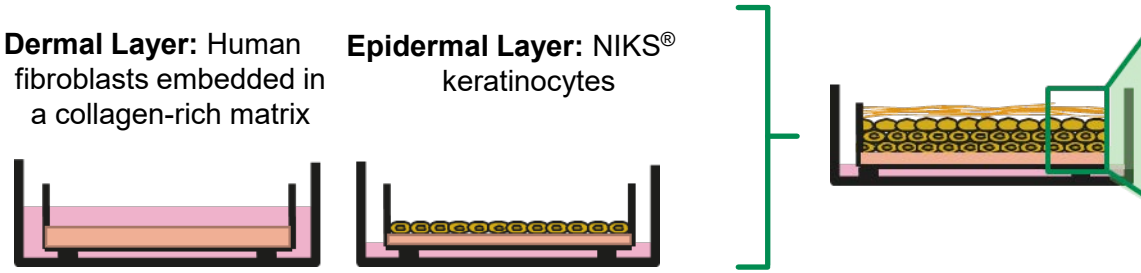
Tissue Manufacturing

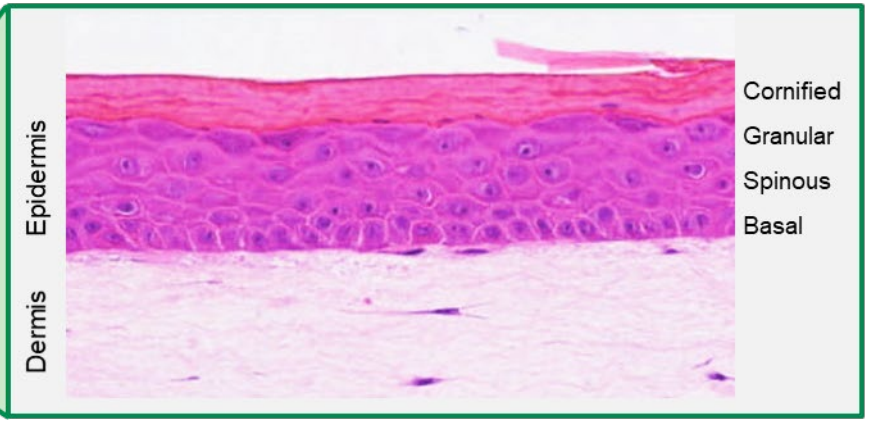
Organotypic Culture

- The cellular components of StrataGraft transform the starting dermal equivalent during the maturation process by synthetizing a structurally organized human ECM

Dermal Layer: Human fibroblasts embedded in a collagen-rich matrix

Epidermal Layer: NIKS® keratinocytes





Multilayered human skin construct

Tissue Characterization

Unique Features

- StrataGraft delivers viable cells that provide a sustained secretion of soluble protein factors that stimulate the body's own ability to heal

Wound-Healing Molecules			Skin ECM Components	
bFGF	GM-CSF	MMP-1	COL I	COL VI
VEGF-A	IL-1α	MMP-3	COL III	Decorin
HGF	IL-6	MMP-9	COL IV	Laminin 332
TGF-β1	IL-8	SDF-1α		
PlGF	IL-10			

- Major structural and functional ECM elements of human skin
- Presence of a basement membrane zone and dermal-epidermal junction
- Sustained secretion of soluble protein factors, including growth factors and cytokines associated with wound healing
- Unlike autograft, once placed, it does not engraft and is gradually replaced by the patient's own cells
- Offers a single-procedure treatment for severe thermal burns

bFGF – basic fibroblast growth factor; COL – collagen; ECM – extracellular matrix; GM-CSF – granulocyte-macrophage colony-stimulating factor; HGF – hepatocyte growth factor; IL – interleukin; MMP – matrix metalloproteinase; PlGF – placental growth factor; SDF-1a – stromal cell-derived factor 1a; TGF-b1 – transforming growth factor b1; VEGF-A – vascular endothelial growth factor A.

1. Harvestine J, Pradhan-Bhatt S, Steiglitz BM, Maher RJ, Comer AR, Gratz KR, Allen-Hoffmann BL. StrataGraft® Skin Tissue, a Bioengineered Regenerative Skin Construct for Severe Acute Wounds. Poster presented at 2020 Biomedical Engineering Society (BMES) Virtual Annual Meeting, October 14–17, 2020.

Severe Thermal Burns Are Associated With a Significant Patient and Societal Burden

500,000 burn injuries receive emergency treatment annually[1]

40,000 require **hospitalization**[2]

~86% are thermal burn cases[3]

10,000 received autografts during the hospital stay[4,5]

Significant burden to patients affecting physical and emotional functions that lead to **reduced QoL**[1,6]

The elderly is an especially **vulnerable population** at increased risk of death[1,6]
Burns are the 8th leading cause of death in those **65 years or older**[1]

Mortality rate rises with the **% TBSA burned**[7]
A 50% case fatality (LD50) occurs once burns are greater than 70% TBSA[7]

Substantial **economic burden** on thermal burn patients who receive inpatient autografts, mainly driven by the initial hospitalization with autograft[4]

Higher %TBSA burned result in greater medical costs and LOS[7]

TBSA – total body surface area; LOS – length of stay; QoL – quality of life

1. Burn Injury Fact Sheet. American Burn Association. https://ameriburn.org/wp-content/uploads/2017/12/nbaw-factsheet_121417-1.pdf. Published February 2018. Accessed July 1, 2020.
2. HCUPnet, Healthcare Cost and Utilization Project. Agency for Healthcare Research and Quality, Rockville, MD. https://hcupnet.ahrq.gov/. Accessed June 5, 2019.
3. Schaefer TJ, Tannan SC. Thermal Burns. [Updated 2020 Jun 7]. In StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; January 2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK430773/.
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Current Treatments of Severe Thermal Burns Require Harvest of Skin From Donor Sites, Resulting in Further Injury

Thermal burns include areas that retain (partial-thickness) and areas that lack (full-thickness) viable dermal elements within the same wound[1]

Autograft is a standard of care for severe thermal burns[2,3] and the most common procedure found in burn-related inpatient stays[4]

When >50% TBSA is burned, the amount of healthy skin available for harvesting is limited. With each re-harvest of healthy skin, the quality of skin decreases.[3]

Multiple skin substitutes for the treatment of severe burns function as a temporary wound cover bridging to autograft for wound closure[5]

Autografting creates a new wound at the harvest site,[5] which has low scar quality 1 year after surgery.[6] Donor site wounds are painful and can create risks of additional scarring and infection.[7-9]

Autografting is especially undesirable in vulnerable patient populations such as the elderly[10,11]

There is a need for alternatives to donor site harvesting for the treatment of severe thermal burns

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The Efficacy and Safety of StrataGraft Was Evaluated in Two Randomized Clinical Studies With an Intrapatient Autograft Comparator

Study Design (Summary)	▶ Two randomized, open label, intrapatient controlled, multicenter clinical studies of 12 months' duration with similar designs: the pivotal **STRATA2016** registration study[1,2] and the supportive **STRATA2011** study[3,4] ▶ **Two comparable wound sites** of each patient were selected and randomized to receive either topical application of StrataGraft or autograft. **Autografts served as the intrapatient control.** ▶ **101 adult patients** with acute thermal burns containing intact dermal elements involving 3-49% TBSA
Coprimary Endpoints*	▶ The **difference in the percent area** of the StrataGraft treatment site and control autograft treatment site that required autografting 3 months following treatment ▶ The **proportion of patients achieving durable wound closure** of the StrataGraft treatment site at 3 months without autograft placement
Secondary Endpoints*	▶ The difference between StrataGraft and autograft donor sites in average **donor-site pain intensity** through Day 14 (FACES) ▶ The difference between StrataGraft and autograft **donor-site scar quality** at Month 3 (POSAS) ▶ The difference between StrataGraft and autograft **treatment-site scar quality** at Month 12 (POSAS)

FACES – Wong-Baker FACES® Pain Rating Scale; POSAS – Patient and Observer Scar Assessment Scale

*Endpoints of the pivotal STRATA2016 study are detailed.

1.StrataGraft® Skin Tissue in the Promotion of Autologous Skin Regeneration of Complex Skin Defects Due to Thermal Burns That Contain Intact Dermal Elements. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03005106. Accessed June 15, 2020.

2. Holmes JH, Shupp JW, Smith DJ, et al. T5: Preliminary analysis of a phase 3 open-label, controlled, randomized trial evaluating the efficacy and safety of a bioengineered regenerative skin construct in patients with deep partial-thickness thermal burns. J Burn Care Res. 2020;41(Supplement_1):S3-S4.

3. StrataGraft® Skin Tissue as an Alternative to Autografting Deep Partial-Thickness Burns. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT01437852. Accessed June 15, 2020.

4. Holmes JH, Schurr MJ, King BT, et al. An open-label, prospective, randomized, controlled, multicenter, phase 1b study of StrataGraft skin tissue versus autografting in patients with deep partial-thickness thermal burns. Burns. 2019;45(8):1749-1758.

StrataGraft Treatment Resulted in Significant Reduction of Donor Site Harvest While Facilitating Durable Wound Closure by Month 3 With a Scar Quality and Safety Profile That Are Comparable to Autograft[1*]

Percent Area Autografted by Month 3†

- The difference in the percent area of StrataGraft and control autograft treatment sites that required autografting by 3 months was **97.8%** ± 16.6% (p<0.0001)
- Donor site harvest was eliminated for **96%** (68/71) of StrataGraft-treated burn sites

Durable Wound Closure by Month 3†

- The proportion of patients achieving durable closure of the StrataGraft treatment site at 3 months without autograft placement was **83.1%** (95% CI: 74.4, 91.8)
- The proportion of patients achieving durable closure of the autograft control treatment site at 3 months without additional autograft placement was **86%** (95% CI: 77.8, 94.0)

Pain Intensity at Donor Site & Scar Quality at Donor and Treatment Sites†

- As a result of elimination of most donor site harvest, **pain intensity through Day 14 and scarring by Month 3** were significantly **reduced at donor sites** (p<0.0001)
- StrataGraft and control autograft achieved clinically **comparable treatment-site scar quality**

Safety

- Overall, the safety profile of StrataGraft with regard to wound-related events, including erythema, swelling, local warmth, and wound site infections, was **similar to that of autograft**
- There were **no reports of rejection to StrataGraft**

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†Results of the pivotal STRATA2016 study are detailed.
CI – confidence interval
1. StrataGraft skin construct [prescribing information]. Madison, WI: Stratatech Corp. Submitted to FDA April 2020.

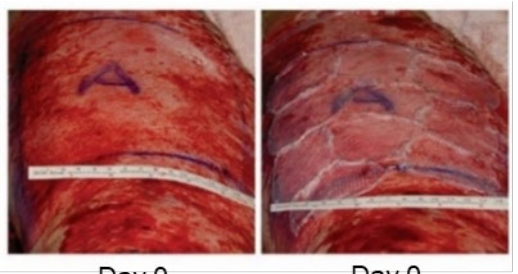
StrataGraft Is Applied to a Surgically Prepared Wound Bed in Appropriate Aseptic Conditions

Topical Application[1]

- Off-white, rectangular sheet of approximately 100 cm^2 (approximately 8 cm by 12.5 cm) that may be trimmed to fit the size and shape of the wound bed
- The number of constructs applied will vary depending on the size of the wound bed
- Each construct is for application to a single patient only
- The constructs can be meshed up to a 1:1 ratio
- The dermal (shiny) side is placed down in contact with the patient's prepared wound bed, ensuring the epidermal (matte) side is facing up
- The construct must have contact across the entire surface of the wound bed
- After application, the construct is anchored to the wound bed in a manner similar to a skin graft and the wound is dressed with a porous, nonadherent contact dressing

Patient Example[2]

- Subject with a thermal burn of 28% TBSA on the upper legs that was prepared by excision of necrotic tissue before receiving StrataGraft



- Treatment site after application of StrataGraft at Day 28, Month 3, and Month 12

1. StrataGraft skin construct [prescribing information]. Madison, WI: Stratatech Corp. Submitted to FDA April 2020.
2. Holmes JH, Schurr MJ, King BT, et al. An open-label, prospective, randomized, controlled, multicenter, phase 1b study of StrataGraft skin tissue versus autografting in patients with deep partial-thickness thermal burns. Burns. 2019;45(8):1749-1758.

Current ICD-10-PCS Codes Do Not Adequately Describe the Application of StrataGraft for the Treatment of Severe Thermal Burns

- When available to patients, StrataGraft will **not require the harvest of donor tissue** to treat most severe thermal burns
- Mallinckrodt Pharmaceuticals submitted an **NTAP application for StrataGraft** to CMS for FY2022 implementation
- Unique ICD-10-PCS codes will facilitate **tracking of the inpatient application of StrataGraft** to adult patients with severe thermal burns

ICD-10-PCS – International Classification of Diseases, 10th Revision, Procedure Coding System; CMS – Centers for Medicare & Medicaid Services; FY – Fiscal Year; NTAP – New Technology Add-on Payment