Original Article

International Physiology
Volume 10 Number 1 January - April 2022
DOI: https://dx.doi.org/10.21088/ip.2347.1506.10122.3

Skin Substitutes: An Overview

Ravi Kumar Chittoria[1], Jacob Antony Chakiath[2]

How to cite this article:

Ravi Kumar Chittoria, Jacob Antony Chakiath/ Skin Substitutes: An Overview/International Physiology.2022;10(1):21–27.

Abstract

Skin substitutes are a heterogeneous group of biologic, synthetic, or biosynthetic materials that can provide coverage of open skin wounds. The aim of skin substitutes is to replicate the properties of the normal skin. Biocompatibility, antimicrobial activity, appropriate hydrophilicity, and biodegradability are all desirable qualities in a skin substitute. The goal of tissue engineering research is to develop cell-based wound substitutes or wound covers that promote cell migration, differentiation, and vascularization to facilitate wound healing.

Keyword: Skin substitute.

INTRODUCTION

The biggest organ on the human body, the skin defends the body from the elements. The loss of the skin barrier's integrity as a result of injury or deformity can result in serious problems or even death. After skin damage, large and deep skin wounds do not heal in a timely manner.[1]

Skin substitutes are a heterogeneous group of biologic, synthetic, or biosynthetic materials that can provide coverage of open skin wounds. The aim of skin substitutes is to replicate the properties of the normal skin. Biocompatibility, antimicrobial activity, appropriate hydrophilicity, and biodegradability are all desirable qualities in a skin substitute.

In this Article, we explain commercially available skin substitutes for different clinical applications. We also call attention to the recent use of 3D bioprinting technology to create cell-based skin substitutes.

Author Affiliation: [1]Professor, Department of Plastic Surgery, [2]Senior Resident, Department of General Surgery, Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry 605006, India.

Corresponding Author: Ravi Kumar Chittoria, Professor, Department of Plastic Surgery, Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry 605006, India.

E-mail: drchittoria@yahoo.com

Received on: 13.04.2022

Accepted on: 30.05.2022

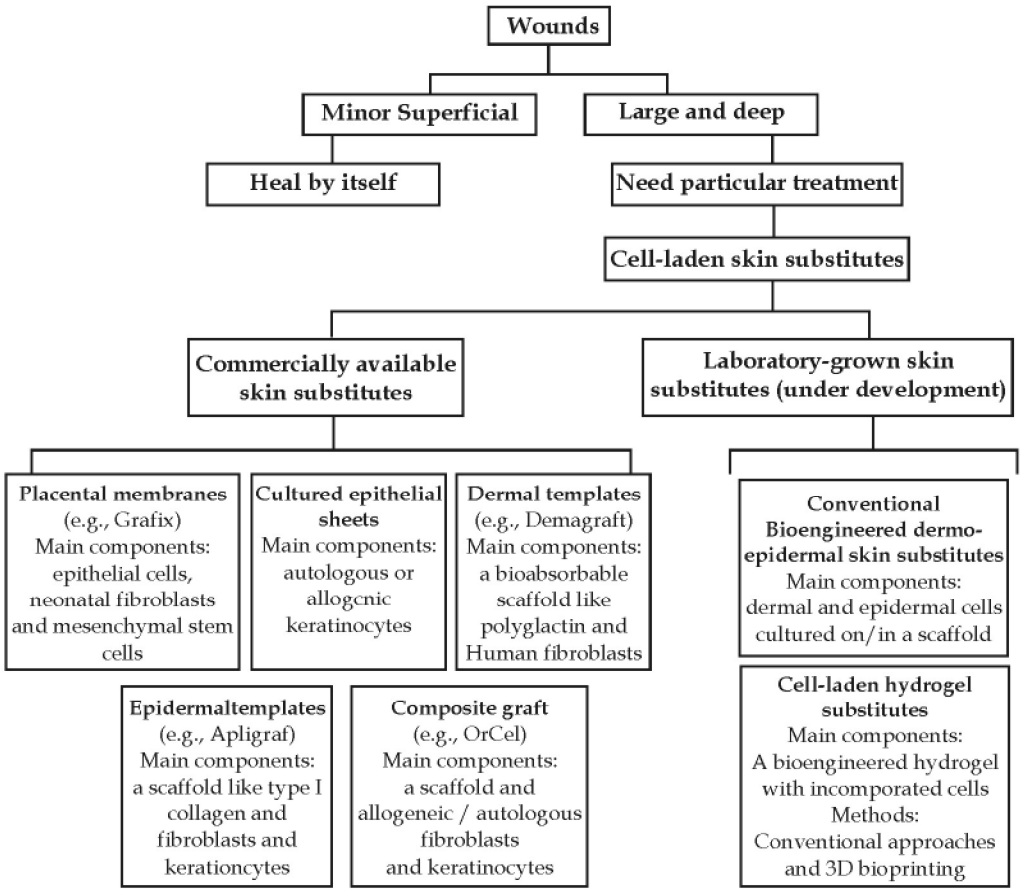
BACKGROUND

Various circumstances can cause skin integrity to be compromised, resulting in a variety of wounds, including acute and chronic wounds. Wounds can also be divided into mechanical injuries such as abrasions and tears produced by external forces, and skin injuries induced by radiation, electricity, corrosive chemicals, and thermal sources causing severe burns.[2]

Minor superficial skin lesions can be healed through epithelialization in the human body without any special therapy. Large and deep skin flaws, on the other hand, necessitate skin replacement in order to heal effectively.[3] Hard-to-heal chronic wounds, impaired vascularization is the main cause of delayed healing.

The goal of tissue engineering research is to develop cell-based wound substitutes or wound covers that promote cell migration, differentiation, and vascularization to facilitate wound healing. The bulk of cell-based skin substitutes are made up of a scaffold that is seeded/cultured with cells.[4]

CLASSIFICATION



CELL-LADEN COMMERCIAL SKIN TEMPLATES

Placental Membranes

Epithelial cells, neonatal fibroblasts, and mesenchymal stem cells (MSCs) in the placental membrane, aid wound healing. MSCs secrete substances that encourage the migration and proliferation of the many cell types involved in wound healing.[5] Hepatocyte growth factor (HGF) and vascular endothelial growth factor (VEGF) are released by MSCs to promote vascular network creation and anti-scarring capabilities, respectively.[6]

Grafix (Osiris Therapeutics Inc., Columbia, MD, USA) is a placental-based cryopreserved allograft that is commercially accessible. It's used to treat diabetic foot ulcers, epidermolysisbullosa, burns, and surgical incisions and dehiscence, among other acute and chronic wounds.[7]

Cultured Epithelial Sheets (CEA)

CEA is made up of either the patient's own keratinocytes (autologous) or donor cells (allografts), which are sheets made from the skin of a stranger. Large burn injuries and persistent ulcers can both benefit from this treatment. Donor skin is limited in burn wounds that cover more than 50% of the total body surface area.[8] As a result, cultivated epithelial autografts may provide covering to aid wound closure. Due to its uneven graft take rates, infection risk, and frequently disappointing

functional and cosmetic results, CEA's application potential is restricted. The lack of a functionally competent dermal component is the primary cause of these issues.[9]

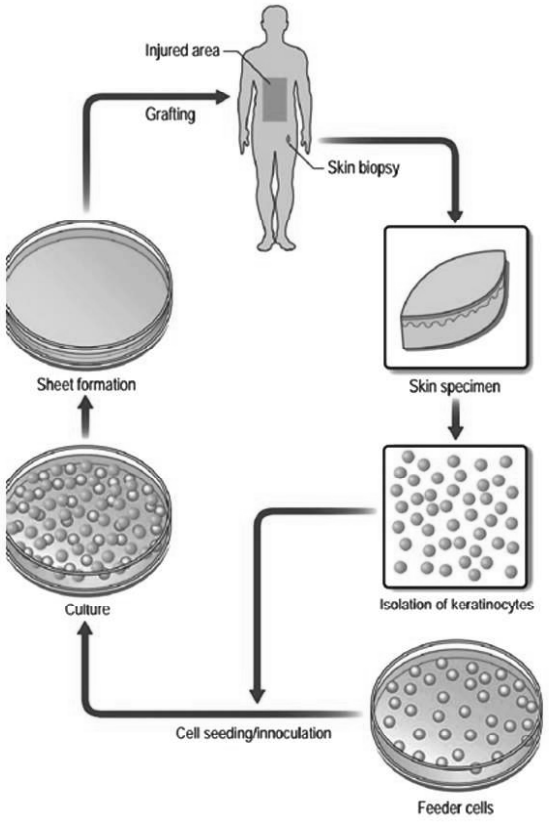


Fig. 1: Keratinocyte culture.

Source: Copyright@Peter C. Neligan plastic surgery principles vol:1

Dermal Templates

Dermagraft is a dermal substitute made up of allogeneic human fibroblasts in a polyglactin scaffold (Smith and Nephew, Largo, FL, USA). It comes frozen in a transparent bag with one piece for a one-time use application. It can be used for lengthy periods of time to treat full-thickness diabetic foot ulcers as well as deep necrotic cutaneous ulcers that do not involve the tendon, muscle, joint capsule, or bone.[10] There are no macrophages, lymphocytes, blood vessels, or hair follicles in dermagraft.[11]

Epidermal Templates

The development of a stratified keratinocyte layer to provide barrier function, is critical focus of epidermal tissue engineering.[12] It acts as a physical scaffold for cell migration and release of soluble substances like chemokines and growth factors.[13] Apligraf (Organogenesis Inc., Canton, Massachusetts, CA, USA) is a bilayered bioengineered skin replacement (BBSS) that mimics the normal structure of human skin by combining a bovine type I collagen lattice with a dermal layer of human fibroblasts and a layer generated by human keratinocytes.[14]

Dermo-Epidermal Skin Equivalents (Composite Graft)

Composite allografts that contain both major skin layers (dermis and epidermis), closely replicating the form and function of normal human skin tissue. In comparison to dermal substitutes, one of the major advantages of composite grafts is their one-step application technique.[15] Many bioengineered commercial composite skin grafts are available likeAlloskin (AlloSource, Centennial, CO, USA) & OrCel (Ortec International, Inc., New York, NY, USA).

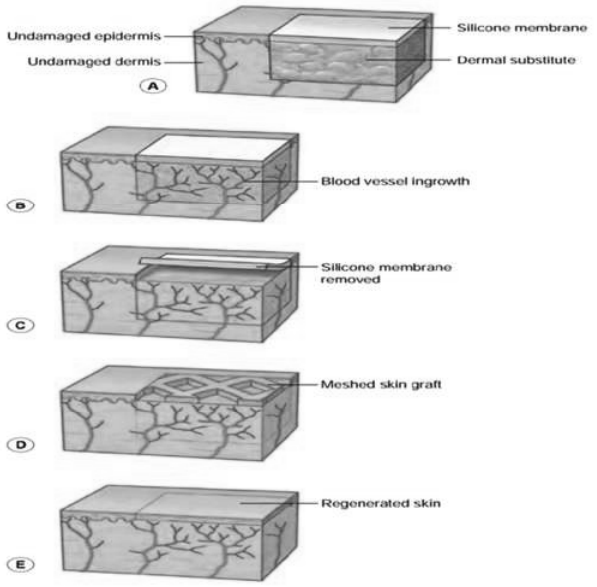


Fig. 2: Skin regeneration with dermal substitutes (Integra)

Source: Copyright@Peter C. Neligan plastic surgery principles vol: 1

BIOENGINEERED DERMO-EPIDERMAL SKIN SUBSTITUTES

(Under Development)

Split and full thickness skin autografts, as well as skin flaps, skin expansion procedures, and dermal replacements, are the "gold standard" approaches for covering such skin abnormalities. For patients with severe, full thickness skin injuries, laboratory-grown skin substitutes offer a fresh, potential therapy alternative.[16,17]

Cell-Laden Hydrogels as Wound Dressings

The most common materials used as a scaffold for culturing cells for skin healing applications are hydrogels. Because of their 3D matrix, which is rich in water, and their biodegradability, hydrogels can be used as a scaffold for cell encapsulation. Moreover, the vast majority of them are biocompatible.[18,19,20]

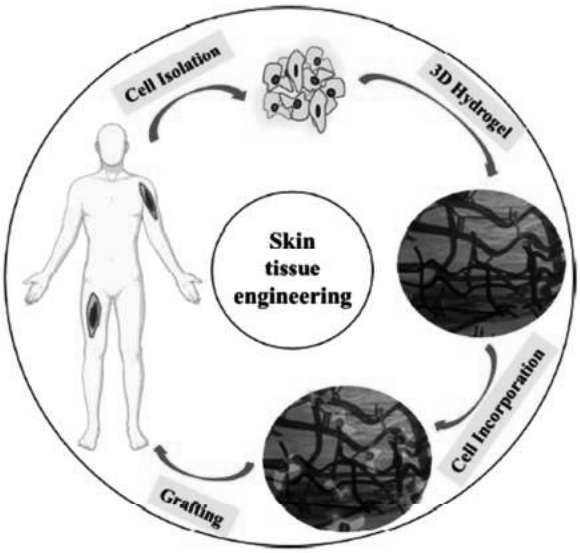


Fig. 3: Schematic representing the preparation process of a cell-laden hydrogel in which cells from an isolated donor are placed and then cultured in a 3D hydrogel matrix and grafted to a skin defect as a skin substitute.

Porous hydrogels are bioscaffolds that include cells, generate a foam or crosslinked hydrogel that can be used as a skin substitute on a wound. Porosity, in particular, is significant because it allowed host cells to infiltrate the 3D network and improving protein transport and diffusion to imitate native tissue structure.[21] The ideal pore size for fibroblast ingrowth is 5–15 m, 20 m for hepatocyte ingrowth, and 20–125 m for adult mammalian skin regeneration.[22,23]

Stimuli-responsive hydrogels, When activated by various internal or external stimuli, the encapsulated cells and biomolecules are released into the host tissue. The development of a cell/ hydrogel scaffold structure in situ allows for the transfer of encapsulated cells, growth factors, and essential nutrients to the wound site via minimally invasive procedures.[24]

In the study conducted by of *Eke et al* [25], to stimulate vascularization in difficult-to-heal wounds, a UV-crosslinked biodegradable hydrogel was used as a scaffold containing adipose-derived stem cells (ADSCs). The hydrogel network was created using methacrylated gelatin (GelMA) and methacrylated hyaluronic acid (HAMA) in this study. After that, a photoinitiator and cells were added to the pre-hydrogel solution at the same time to induce photo-crosslinking.[25]

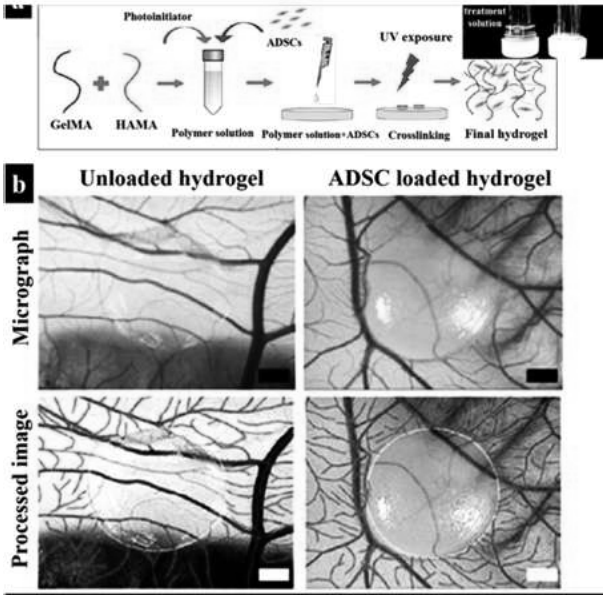


Fig. 4: Schematic demonstrating methacrylated gelatin (GelMA) acid methacrylated hyaluronic acid (HAMA) chain integration to prepare polymer solution. Furthermore, the addition of photoinitiator to prepare a UV-crosslinkable hydrogel containing adipose-derived stem cells (ADSCs) to produce a cell-laden hydrogel wound 25.

3D Bioprinting of Cell-Laden Hydrogels for Wound Dressings

A new fabrication technology for cell-laden hydrogels is 3D printing. This technique comprises layer-by-layer printing of hydrogel with cells to create a complicated bioscaffold.[25] The capacity to produce therapeutically relevant skin constructs that closely replicate native skin architecture and heterogeneity is the main benefit of this technology in skin engineering. However there are a variety of hydrogels used in bioprinting, natural polymers such as alginate, collagen, gelatin, fibrin, and hyaluronic acid are the most common.[26,27]

Several studies have shown that a human-plasma derived bilayered skin used for the treatment of burn injuries and traumatic and surgical wounds. other ones are Neonatal human epidermal keratinocytes (NHEKs) and neonatal human dermal fibroblasts (NHDFs), both embedded in a fibrin–collagen hydrogel matrix known as Apligraf.[28] In These studies, wound-healing behaviour of the control (no therapy) and Apligraf

(described previously) groups were compared. Wounds treated with printed substitutes took 14–16 days to heal, compared to 21 days for the control group and 28 days for the Apligraf group.[29] Furthermore, histological analysis revealed the production of dermal and epidermal skin layers that are equivalent to native skin, as well as the appearance of new microvessels in mouse tissue.[30]

Other recent research projects have focused on producing cell-laden hydrogel bioinks to print skin layers or substitutes, with natural hydrogels as the focus. A suitable hydrogel bioink should be cell friendly and capable of incorporating/ encapsulating cells both before and after crosslinking. To create adequate cues for cells to differentiate and proliferate, the bioink hydrogel should resemble the physical and mechanical properties of original skin after printing.[31,32]

An Ideal skin coverage should not only protect the wound and promote tissue regeneration, but it should also improve the aesthetics, satisfaction, and welfare of the patients. As a result, significant progress has been made in the field of skin tissue engineering in recent years. To identify the ideal skin replacement for use in acute and chronic skin wounds, many skin substitutes based on synthetic or natural scaffolds, as well as bioengineered skin replacements, have been created.3D bioprinting has evolved as a practical way for fabricating skin substitutes from primary cells derived from the patients' own skin cells.

These various techniques to developing newer skin substitutes provide new optimism that the optimal skin substitute may be developed shortly.

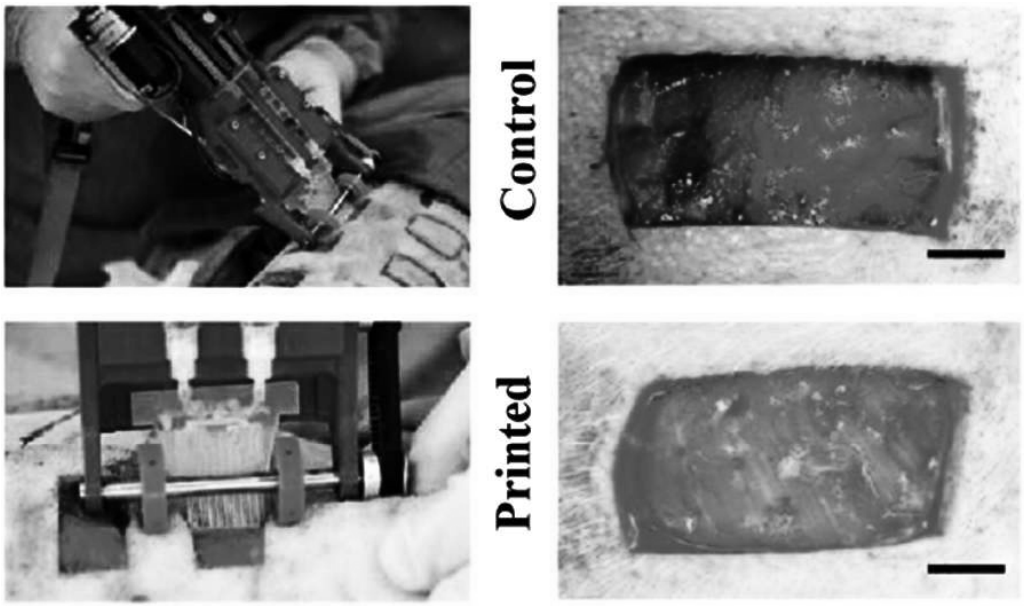


Fig. 5: Handheld skin printer. Above image shows in situ deposition of a fibrin–hyaluronic acid/ collagen sheet on top of a full-thickness excisional porcine wound using a handheld skin printer. (top) Close-up view of sheet formation within wound bed with a 2 cm microfluidic cartridge (bottom)[32]

Table 1: Explain the available permanent and temporary dermal & epidermal grafts.

Product	Tissue-Cells	Manufacturing Avilability	Origin
Epicel® (Genzyme MA)	Epidermis Cultured Epidermd Autograft (CEA) Sheets	Tissue Cultures Expanded In The Labortory Our Several Weeks	Autologous And Exnoogenic (Residual Amounts Pf Murine Cells
Recell®(Avita Medical,UK)	Epidermis -Autologous Epicermal Cells Dermisfibroblasts; Cells Suspension, Dilvered With Spray	Bedside Approach (About 30 Minutes Required)	Autologous
Cellutone®Epidermal Harvesting System (KCI, TX)	Epidermis-Autologous Epidermal Islands Delivered On A Dressing	Bedside Approach (About 60 Minutes Required)	Autologous

Integra® (Integra Lifesciences, NJ)	Dermis-Bovine Tendon Type I Collagen And Glycosaminoglycans On A Silicone	On The Shelf	Autologous
Matriderm® (Medskin Solutions Dr. Sewelack, Germany)	Dermis-Bovine Acellular Non-Crosslinked, Coated With Elastin	On The Shelf	Xenogeneic
Alloderm® (life Cell Coporation, NJ)	Dermis-Human Acellular Lyophilized Cadaver Dermis	On The Shelf	Allogeneic
Dermagraft® (Organogensis, MA)	Dermis-Human Fibroblasts On Polyglycolic-Polylactic Acid Mesh	On The Shelf	Allogeneic
EZ Derm (Molnlycke Health Care, Sweden)	Dermis-Porcine Aldehyde Cross-Linked Dermal Collagen	On The Shelf	Xenogeneic
Oasis® Matrix (Smith And Nephew, TN) Allograft	Dermis-Porcine Acellular Small Intestine Submucosa. Composite -Cryopreserved Cadaveric Skin	On The Shelf	Xenogeneic
Apligraf® (Organogenesis, MA)	Composite-Neonatal Human fibroblasts In Bovine Type I Collagen Neonatal Human Keratinocytes	On The Shelf	Allogeneic / Xenogeneic

Source: copyright@Peter C. Neligan plastic surgery principles vol: 1

REFERENCES

1. Shevchenko, R.V.; James, S.E. A review of tissue-engineered skin bioconstructs available for skin reconstruction. J. R. Soc. Interface 2009, 7, 229–258. [CrossRef] [PubMed]
2. Rowan, M.P.; Cancio, L.C.; Elster, E.A.; Burmeister, D.M.; Rose, L.F.; Natesan, S.; Chan, R.K.; Christy, R.J.; Chung, K.K. Burn wound healing and treatment: Review and advancements. Crit. Care 2015, 19, 1–12. [CrossRef] [PubMed]
3. Klar, A.S.; Michalak-Mi´cka, K.; Biedermann, T.; Simmen-Meuli, C.; Reichmann, E.; Meuli, M. Characterization of M1 and M2polarization of macrophages in vascularized human dermo-epidermal skin substitutes in vivo. Pediatr. Surg. Int. 2017, 34, 129–135. [CrossRef]
4. Pogorielov, M.; Hapchenko, A.; Pogorielov, O.O.M. Tissue Engineering: Challenges and Selected Application. Adv. Tissue Eng.Regen. Med. Open Access 2017, 3, 1–6. [CrossRef]
5. Olena, P.; Prokopyuk, V.; Figueiredo, C.; Pogozhykh, D. Placenta and Placental Derivatives in Regenerative Therapies: Experimental Studies, History, and Prospects. Stem Cells Int. 2018, 2018, 1–14. [CrossRef]
6. Maxson, S.; Lopez, E.A.; Yoo, D.; Danilkovitch-Miagkova, A.; Leroux, M.A. Concise Review: Role of Mesenchymal Stem Cells in Wound Repair. STEM CELLS Transl. Med. 2012, 1, 142–149. [CrossRef]
7. Lavery, L.A.; Fulmer, J.; Shebetka, K.A.; Regulski, M.; Vayser, D.; Fried, D.; Kashefsky, H.; Owings, T.M.; Nadarajah, J. The Grafix Diabetic Foot Ulcer Study Group The efficacy and safety of Grafix® for the treatment of chronic diabetic foot ulcers: Results of a multi-centre, controlled, randomised, blinded, clinical trial. Int. Wound J. 2014, 11, 554–560. [CrossRef] [PubMed]
8. Wood, F.M.; Kolybaba, M.; Allen, P. The use of cultured epithelial autograft in the treatment of major burn wounds: Eleven years of clinical experience. Burns 2006, 32, 538–544. [CrossRef] [PubMed]
9. Barret, P.J.;Wolf, S.E.; Desai, M.H.; Herndon, D.N. Cost-Efficacy of Cultured Epidermal Autografts in Massive Pediatric Burns. Ann. Surg. 2000, 231, 869–876. [CrossRef]
10. Marston, W.A.; Hanft, J.; Norwood, P.; Pollak, R. The Efficacy and Safety of Dermagraft in Improving the Healing of Chronic Diabetic Foot Ulcers: Results of a prospective randomized trial. Diabetes Care 2003, 26, 1701–1705. [CrossRef]
11. 11. Hart, C.E.; Loewen-Rodriguez, A.; Lessem, J. Dermagraft: Use in the Treatment of Chronic Wounds. Adv. Wound Care 2012, 1, 138–141. [CrossRef]
12. Kumar, S.; Kang, H.J.; Berthiaume, F. Scaffolds for epidermal tissue engineering. In Handbook of Tissue Engineering Scaffolds; Woodhead Publishing: Cambridge, UK, 2019; Volume 2, pp. 173–191.
13. Curran, M.P.; Plosker, G.L. Bilayered Bioengineered Skin Substitute (Apligraf®): A Review of Its Use in the Treatment of Venous Leg Ulcers and Diabetic Foot Ulcers. BioDrugs2002, 16, 439–455. [CrossRef] [PubMed]
14. Pourmoussa, A.; Gardner, D.J.; Johnson, M.B.; Wong, A.K. An update and review of cell-based wound dressings and their integration into clinical practice. Ann. Transl. Med. 2016, 4, 457. [CrossRef]
15. Braziulis, E.; Biedermann, T.; Hartmann-Fritsch, F.; Schiestl, C.; Pontiggia, L.; Böttcher-Haberzeth, S.; Reichmann, E.; Meuli, M.Skingineering I:

Engineering porcine dermo-epidermal skin analogues for autologous transplantation in a large animal model.Pediatr. Surg. Int. 2011, 27, 241–247. [CrossRef]

16. Schiestl, C.; Neuhaus, K.; Biedermann, T.; Böttcher-Haberzeth, S.; Reichmann, E.; Meuli, M. Novel Treatment for Massive Lower Extremity Avulsion Injuries in Children: Slow, but Effective with Good Cosmesis. Eur. J. Pediatr. Surg. 2010, 21, 106–110. [CrossRef]
17. Schiestl, C.; Stiefel, D.; Meuli, M. Giant naevus, giant excision, eleg (i) ant closure? Reconstructive surgery with Integra ArtificialSkin® to treat giant congenital melanocytic naevi in children. J. Plast. Reconstr. Aesthet. Surg. 2010, 63, 610–615. [CrossRef]
18. Zimoch, J.; Padial, J.S.; Klar, A.S.; Vallmajo-Martin, Q.; Meuli, M.; Biedermann, T.; Wilson, C.J.; Rowan, A.; Reichmann, E. Polyisocyanopeptide hydrogels: A novel thermo-responsive hydrogel supporting pre-vascularization and the development of organotypic structures. ActaBiomater. 2018, 70, 129–139. [CrossRef]
19. Tavakoli, S.; Kharaziha, M.; Nemati, S.; Kalateh, A. Nanocomposite hydrogel based on carrageenan-coated starch/cellulose nanofibers as a hemorrhage control material. Carbohydr. Polym. 2021, 251, 117013. [CrossRef]
20. Tavakoli, S.; Kharaziha, M.; Kermanpur, A.; Mokhtari, H. Sprayable and injectable visible-light Kappa-carrageenan hydrogel for in-situ soft tissue engineering. Int. J. Biol. Macromol. 2019, 138, 590–601. [CrossRef] [PubMed]
21. Rana, D.; Kumar, T.S.; Ramalingam, M. Cell-laden hydrogels for tissue engineering. J. Biomater. Tissue Eng. 2014, 4, 507–535.[CrossRef]
22. Q.; Mai, Y.-W. Biomaterials for Implants and Scaffolds. In Biomaterials Science and Engineering; Springer: Berlin, Germany, 2017; Volume 8, ISBN 978-3-662-53572-1.
23. Klawitter, J.J.; Hulbert, S.F. Application of porous ceramics for the attachment of load bearing internal orthopedic applications. J.Biomed. Mater. Res. 1971, 5, 161–229. [CrossRef]
24. Yeh, J.; Blumling, J.; Karp, J.M.; Gantz, J.; Chandawarkar, A.; Eng, G.; Iii, J.B.; Langer, R.; Khademhosseini, A. Micromolding of shape-controlled, harvestable cell-laden hydrogels. Biomaterials 2006, 27, 5391–5398. [CrossRef] [PubMed]
25. Eke, G.; Mangir, N.; Hasirci, N.; MacNeil, S.; Hasirci, V. Development of a UV crosslinked biodegradable hydrogel containing adipose derived stem cells to promote vascularization for skin wounds and tissue engineering. Biomaterials 2017, 129, 188–198. [CrossRef]
26. Murphy, S.V.; Atalaa, A. 3D bioprinting of tissues and organs. Nat. Biotechnol. 2014, 32, 773–785. [CrossRef]
27. Li, H.; Tan, C.; Li, L. Review of 3D printable hydrogels and constructs. Mater. Des. 2018, 159, 20–38. [CrossRef]
28. Hng, G.; Li, F.; Zhao, X.; Ma, Y.; Li, Y.; Min, L.; Jin, G.; Lu, T.J.; Genin, G.M.; Xu, F. Functional and Biomimetic Materials for Engineering of the Three-Dimensional Cell Microenvironment. Chem. Rev. 2017, 117, 12764–12850. [CrossRef] [PubMed]
29. Yanez, M.; Rincon, J.; Dones, A.; De Maria, C.; Gonzales, R.; Boland, T. In Vivo Assessment of Printed Microvasculature in a Bilayer Skin Graft to Treat Full-Thickness Wounds. Tissue Eng. Part A2015, 21, 224–233. [CrossRef]
30. Albanna, M.; Binder, K.W.; Murphy, S.V.; Kim, J.; Qasem, S.A.; Zhao, W.; Tan, J.; El-Amin, I.B.; Dice, D.D.; Marco, J.; et al. In SituBioprinting of Autologous Skin Cells Accelerates Wound Healing of Extensive Excisional Full-Thickness Wounds. Sci. Rep. 2019,9, 1–15. [CrossRef] [PubMed]
31. Hafezi, F.; Scoutaris, N.; Douroumis, D.; Boateng, J.S. 3D printed chitosan dressing crosslinked with genipin for potential healingof chronic wounds. Int. J. Pharm. 2019, 560, 406–415. [CrossRef]
32. Admane, P.; Gupta, A.C.; Jois, P.; Roy, S.; Lakshmanan, C.C.; Kalsi, G.; Bandyopadhyay, B.; Ghosh, S. Direct 3D bioprintedfullthicknessskin constructs recapitulate regulatory signaling pathways and physiology of human skin. Bioprinting2019, 15, e00051.[CrossRef]