Table 1: Key contributing cells and factors involved in the phases of wound healing.

Haemostasis	**Inflammation**	**Proliferation**	**Remodelling**
TYPICAL TIMING			
Hours	4-5 days	Up to 14 days	Lasts 12-18 months
KEY CONTRIBUTING CELLS[5,12]			
Keratinocytes	Neutrophils	Macrophages	T-lymphocytes
Endothelial	Monocytes	Fibroblasts	Fibroblasts
Platelets	Macrophages	Myofibroblasts	Myofibroblasts
	Endothelial cells	T-lymphocytes	
	Fibroblasts		
KEY CONTRIBUTING CYTOKINES[4,13]			
IL-1	EGF	EGF	TGF-β
TXA2	PDGF	VEGF	PDGF
TGF-α	TGF-β	TGF-β	IGF
TGF-β	FGF	PDGF	
PDGF	IFN-α	FGF	
EGF	TNF-α	IL-6	
VEGF	IL-1		
FGF	IL-8		
	IL-10		

Table 2: The classification of skin substitutes according to their biological actions. Adapted from Horch *et al*.[16]

Types of skin substitutes	Definition
Temporary	Materials which can be placed on a fresh wound (usually partial thickness) and left until healed
Semi-permanent	Materials which are left attached to the excised wound, and eventually added upon with autologous skin grafts in a two staged surgical procedure.
Permanent	Incorporating an epidermal analogue, dermal analogue, or both as a permanent skin replacement solution

Table 3: Current available commercial tissue engineered therapies for wound healing.

Commerical Products	Product Composition
Acellular products	
Biological matrix	
Promogram™ (Acelity L.P. Inc, SA, USA)	Oxidized regenerated cellulose and collagen
Puraply® (Organogenesis Inc, MA, USA)	Porcine-derived type 1 collagen
MatriDerm® (MedSkin Solutions Dr. Suwelack AG, Germany)	Bovine collagen fibrils with elastin
Tisseel® (Baxter International Inc, USA)	Fibrin
Beriplast P (CSL Behring, PA, USA)	Freeze-dried fibrinogen-factor XIII and thrombin
EVICEL® (Ethicon, NJ, USA)	Fibrin
Hyaff® (ATGmed - AT Technologies GmbH, Germany)	Hyaluronic acid
Hycoat® (The Hymed Group, Bethlehem, PA)	Sodium hyaluronate
Synthetic/Biosynthetic matrix	
Integra® (Integra Life Sciences Corp, NJ, USA)	Bilayer matrix bovine collagen and silicon
Hyalomatrix® (Anika Therapeutics, MA, USA)	Silicon membrane bound to hyaluronic acid
Biobrane® (Mylan and Smith & Nephew, FL, USA)	Silicon membrane bound to porcine collagen coated nylon mesh
Suprathel® (Polymedics Innovation)	D.Lactide trimethylene carbonate and epsilon-capronolactone membrane
Terudermis (Olympus Terumo Biomaterial Corp. Tokyo, Japan)	Bovine dermal cross-linked atelocollagen with or without silicone.
Pelnac (Gunze Ltd, Medical Materials Centre, Kyoto, Japan)	Procine tendon derived atelocollagen type I with or without silicone film.
Biologically processed matrix	
OASIS Wound Matrix® (Cook Biotech Inc, IN, USA)	Acellular procine small intestinal submucosa
PriMatrix® (Integra Life Science Corp, MA, USA)	Acellular fetal bovine dermis
MatriStem® (ACell Inc, MD, USA)	Acellular porcine urinary bladder

SurgiMend® (Integra Life Science Corp, MA, USA)	Acellular fetal or neonatal bovine dermis
AlloDerm® (LifeCell Corp., Branchburg, NJ, USA)	Acellular human dermis
GraftJacket® (Wright Medical Technology Inc, TX, USA)	Acellular human dermis
DermaMatrix® (Musculoskeletal Transplant Foundation and Synthes CMF, PA, USA)	Acellular human dermis
EZ Derm® (Mölnlycke Health Care, LLC, GA, USA)	Acellular silver-impregnated aldehyde cross-linked porcine dermis
Amnioexcel (Derma Sciences Inc, NJ, USA)	Dehydrated amnion-derived tissue
Biovance® (Alliqua BioMedical Inc, PA, USA)	Dehydrated amnion-derived tissue
Grafix® (Osiris Therapeutics Inc, MD, USA)	Cryopreserved amnion-derived tissue
Epifix®/EpiBurn® (MiMedx Group Inc, GA, USA)	Dehydrated and sterilised human amnion/chorion tissue

Cellular products

Epidermal products

Epicel® (Genzyme Tissue Repair Corporation, MA, USA)	Cultured autologous keratinocytes
Keratinozyten Sheets (DIZG, Berlin, Germany)	Cultured autologous keratinocytes
ReCell® (Avita Medical, UK)	Autologous epidermal cells in liquid suspension
MySkin (Celltran Ltd, Sheffield, UK)	Cultured autologous keratinocytes on membrane
Laserskin®/Vivoderm® (Fidia Advanced Biopolymers, Padua, Italy)	Cultured autologous keratinocytes in laser perforated hyaluronic acid

Dermal/Epidermal-dermal (Composite) products

Theraskin (Soluble Systems LLC, VA, USA)	Human allogeneic split-skin graft including keratinocytes and fibroblast
Dermagraft® (Organogenesis Inc, MA, USA)	Neonatal foreskin-derived fibroblast seeded in polyglycolic acid or polyglactin-910 mesh
Apligraf® (Organogenesis Inc, MA, USA)	Bilayered human neonatal epidermal keratinocytes and neonatal foreskin-derived fibroblast seeded in bovine collagen matrix
StrataGraft® (Stratatech Corp, WI, USA)	Bilayered human dermal fibroblast and human keratinocyte derived fully stratified epidermis

Growth factor products

	Human recombinant platelet-derived growth factor
Regranex® (Ortho-McNeil, NJ, USA)	
Autologel® (Cytomedix, Inc, MD, USA)	Platelet-rich plasma

Table 4. Cell types used in the studies systematically reviewed.

Cell type	Number of studies	Reference
Bone marrow derived stem cells	31	41–69
Adipose derived stem cells	16	54,65,66,70–81
Endothelial cells/endothelial progenitor cells	5	53,75,82–84
Umbilical cord MSCs	4	65,85–87
Whartons Jelly MSCs	4	88–91
Fibroblasts	3	66,92,93
Keratinocytes	2	94,95
Circulating cells	2	96,97
Skin derived stem cells	1	98,99
Stromal vascular fraction	1	100
Amniotic fluid stem cells	1	101
Pluripotent stem cells	1	102
Human urine derived stem cells	1	103
Myeloid cells	1	104
Pancreas or submandibular derived stem cells	1	105
Endometrial Regenerative cells	1	106

Table 5. Summary of all growth factors used in the studies systematically reviewed.

Growth factor	Number of studies	References
SDF-1- alpha	8	42,50,51,65,74,102,146,147
VEGF	8	65,83,102,148–152
bFGF/FGF	11	55,65,83,102,149,153–158
Human epidermal growth factor	4	159–162
Neutrophin-3	1	163
Angiopoietin-1	1	43
Conditioned media	6	85,87,89–91,163,164
Glucose oxidase	1	165
Platelet rich plasma / platelet lysate	4	46,166–168
Hepatocyte growth factor	1	168
Platelet derived growth	4	55,65,83,169
TNF	2	65,102
Thrombin	1	170
Substance P	2	84,171
Other	14	45,56,72,84,97,102,103,154,172–177

Table 6. Summary of the clinical trial data, that uses MSCs and ECM scaffolds.

Ref.	n	Wound type	Scaffold	Cell Source	Treatment	Results
[183]	1	Idiopathic lower leg ulcer	Terudermis	Autologous BM aspirate	BM cell suspension in collagen matrix direct to wound.	Good granulation tissue at 2 weeks, at which point STSG with 100% take.
[184]	20	4 trauma 2 venous ulcers 3 burns 11 decubitus ulcers	Pelnac	Autologous BM aspirate	1) 9 cases: MSC + collagen matrix only direct to wound. 2) 5 cases: MSC + matrix, subsequent STSG. 3) 6 cases: Diced FTSG, then MSC + matrix on top.	1) 7 healed 8 weeks; 2 burns patients mostly healed. 2) 3 healed within 3 weeks after application of MSC + matrix; 2 healed after 2 applications. 3) 4 healed within 8 weeks; 2 died of unrelated pathology before end of study, but partially healed.
[185]	8	All diabetic foot ulcers	Surgicoll	Autologous BM aspirate	BM cell suspension injected into a debrided wound bed. Suspension, platelet growth factors and fibrin glue mixture applied and allowed to clot. Suspension impregnated collagen matrix was placed on top.	3 patients: complete healing of wound. 5 patients: significantly decreased in size (% decrease in wound area average: 57%; range 24-79% decrease)