Table 6.1 List of Biological and Composite Skin Substitutes

Materials	Composition	Thickness	Brand	Indication
Biological				
Alloderm	Acellular human dermis	0.79–3.3 mm	Lifecell Corporation, NJ, USA	Burns, soft tissue defects
Allomax	Acellular human dermis	0.8–1.8 mm	Bard Davol, RI, USA	Soft tissue defects
DermaMatrix	Acellular human dermis	0.2–1.7 mm	Synthes, PA, USA	Soft tissue defects
Glyaderm	Acellular human dermis	0.2–0.6 mm	Beverwijck, The Netherlands	Full thickness wounds
Graftjacket	Acellular human dermis	1; 1.4; 2 mm	Wright Medical Technology, TN, USA	Soft tissue defects
Oasis	Porcine small intestine submucosa acellular collagen	0.15–0.3 mm	Healthpoint Ltd, TX, USA	Burns, chronic wounds
Permacol	Acellular porcine dermis	0.4 or 1.5 mm	Covedien, OH, USA	Full thickness wounds
Strattice	Acellular porcine dermis	1.5–2 mm	LifeCell, NJ, USA	Soft tissue reconstruction
SurgiMend	Acellular bovine dermis	0.4–1.54 mm	TEI Biosciences, MA, USA	Soft tissue reconstruction
Tiscover	Acellular human dermis autologous FB	1–2 mm	A-SKIN, BV, The Netherlands	Chronic wounds
Xenoderm	Acellular porcine dermis	0.3 mm	MBP Neustadt, Germany	Full thickness wounds
Composite				
Apligraf	Allogenic neonatal FB	0.4 mm	Organogenesis, MA, USA	Donor sites, EB
	Allogenic neonatal KC	0.75 mm		
Dermagraft	Mesh + allogenic FB	0.19 mm	BioHealing, CA, USA	Wounds, diabetic ulcers
Hyalomatrix	Hyaluron-based scaffolds with autologous FB	1.2 mm	Fidia	Burns, chronic wounds
Integra	Human collagen I with GAG and silicone top	1.3 mm	Integra Life Sciences, NJ, USA	Burns, chronic wounds
Matriderm	Bovine collagen I, elastin	1 and 2 mm	Care AG, Germany	Burns, chronic wounds
OrCel previously CCS	Collagen I sponge gel allogenic FB and KC	1 mm	Ortec International, NY, USA	Chronic wounds, donor sites
Renoskin	Bovine collagen I and GAG	1.5–2.5 mm	Perouse Plastie, France	Burns, defects
Terudermis	Calf collagen polyester mesh ± silicone top	4 types	Olympus Terumo Biomaterials, Japan	Burns, mucosal defects
TransCyte	Collagen with neonatal FB nylon mesh + silicone top	1.2 mm	Sciences, Inc, CA, USA	Burns

The composition of the substitute is represented in column 2, the thickness of the substitute is shown in column 3. Note that not all these substitutes are available worldwide. Also, they may not be approved for the same indication in different countries. None of the engineered cell-containing skin substitutes has been approved for the European market. FB = fibroblast, KC = keratinocyte, GAG = glycosaminoglycan

within a 2-week timespan, similar to an allograft in a clinical setting. Consequently it is the growth-factor boost of these allogenic cells in the wound-healing environment that may accelerate repair, and not the cells as such. On the other hand, if autologous cells are seeded into the substitute, the handling protocol becomes elaborate because the cells must be obtained from an autologous biopsy. Therefore, the processing of these substitutes is very costly and time-consuming.

Because of these parameters, more studies are required to evaluate the added value of compound substitutes in a clinical context, compared to full-thickness skin grafts on a surgically prepared wound-bed. It seems probable however, that the next generation of off-the-shelf full-thickness skin substitutes will emerge from these scientific data.

DE-NOVO ASSEMBLY OF MATRICES

In order to mimic structural and functional properties of human extracellular matrix, new techniques are being developed. The electrospinning of polymeric nanoscale-fibers such as collagen has shown excellent results and this technique is relatively easy and inexpensive.[50] Collagen nanofibrous scaffolds possess a structure mimicking native

extracellular matrix. They possess excellent biocompatibility with similar cellular organization, proliferation and maturation compared with current techniques such as freeze-dried collagen.[51]

The future in ready-to-wear custom-made skin requires enormous advances in the field of extracellular matrix biology, since these skin substitutes should thrive in aberrant healing conditions when vascularization is impaired, chronic inflammation exists, or proteinases are abundantly present; e.g. in a diabetic patient, under cytostatic drugs or corticosteroids.

Adding biomolecular cues of wound healing and tissue regeneration to the 3-D scaffold might anticipate these adverse healing events creating a "smart" tissue-scaffold in which tissues migrate, integrate, and proliferate.[52–55]

URETHRA AND BLADDER

Approximately 400 million people worldwide suffer from urinary bladder cancer. When radical cystectomy is performed, the intestine is frequently used for urinary bladder reconstruction. However, complication rates up to 56% are reported.[56]

Atala *et al* treated seven patients in need of a cystoplasty using adult autologous urothelial and muscle cells from a bladder biopsy grown in culture. These cells were seeded on a biodegradable bladder-shaped scaffold made of collagen, or a composite of collagen and polyglycolic acid (PGA). About 7 weeks after the biopsy, the engineered bladder was used for reconstruction and implanted either with or without an omental wrap. They reported excellent results in a follow-up period of 22–61 months.[57] Postoperatively, the mean bladder leak-point pressure decrease at capacity, and the volume and compliance increase were greatest in the composite engineered bladders with an omental wrap.

Nevertheless, the construction of neo-bladder for patients with muscle-invasive bladder cancer is much more challenging because of the inability to use autologous stem cells derived from the urinary tract.[58] This limitation demands searching for new sources of stem cells.

Raya-Rivera *et al* reported a clinical tissue-engineering strategy to restore long defects of the urethra in 5 patients. They cultivated smooth muscle cells and epithelial cells obtained from bladder biopsies. These cells were cultured for 1 week to ensure migration, proliferation, and matrix production and were then seeded onto tubular PGA: polylactide-co-glycolide-acid (PLLA-PGA) scaffolds. The authors confirmed that tissue organization of these scaffolds was to native tissue. They reported excellent functional flow rates at 36–76 months.[59]

In 1990, Romagnoli *et al* reported two patients treated with cell sheets of serially cultivated autologous urethral mucosal cells to treat posterior hypospadias.[60] No scaffold was used. The cells were directly applied in situ and mounted on petrolatum gauze. The reported physiological function at follow-up after 6 and 18 months was excellent.

BONE

Quarto *et al* seeded expanded osteoprogenitor cells on a macroporous hydroxyapatite matrix to treat long bone defects in three patients of various ages. In a follow-up of 15 to 27 months, they reported abundant callus formation along the implant and good integration with the host bone by the second month after surgery.[61]

Warnke *et al* used a cell-based strategy to treat mandibular defects after oncological resection. The authors used a titanium mesh-cage filled with bone-mineral segments. They added bone-morphogenetic proteins and bone marrow.[62] The construct was matured into the latissimus dorsi muscle for seven weeks. The group reported a substantial improvement in quality of life of the patient. Despite exposure to oral flora due to fracture of the titanium mesh and partial infection of the regenerated bone, the mandible replacement retained its function over 13 months after transplantation.[63]

TRACHEA

The trachea has a longitudinal flexibility and lateral rigidity to withstand the rigors of negative pressures during respiration and to allow mobility during deglutition, speech and movements of the neck. Moreover, the trachea has a well-vascularized mucosal lining that serves as a primary host defense mechanism against toxic particles present in air.[12]

At first sight, it may appear relatively easy to generate a hollow tube that mimics the windpipe. However it is very complex to create a long, Pleonasm flexible vascularized tube that has a mucosal lining with ciliated epithelium.[64]

Delaere *et al* used a trachea allotransplantation strategy to restore long-segment defects of the trachea. A donor trachea was prelaminated in the forearm and native allogenic mucosa was replaced with recipient mucosa.[65] This allowed for stopping of immunosuppression after orthotopic transfer to the defect in a second stage.[66] Using their prelamination protocol as a vascular platform, they currently investigate decellularization of the allotrachea to further diminish immunogenicity and autologous cell-cultivation to induce faster re-epithelialization.[12]

Kojima and Vacanti reported in 2004 a strategy forming a tube with sheets of bioresorbable PGA seeded with autologous fibroblasts and chondrocytes from the nasal septa of sheep. This construct was then implanted under the sternocleidomastoid muscle to allow for extrinsic vascularization.[67] The concept was innovative but unfortunately grafts collapsed upon orthotopic transfer.

Omori *et al* reported in 2005 the first human case applying regenerative medicine principles to partially restore the cricoid cartilage and cervical trachea.[68] They used an acellular biosynthesized polypropylene-reinforced mesh coated with collagen and preclotted with autologous blood, in four human cases with a 8- to 34-month follow-up. In a canine model, the same group added fibroblasts and bone marrow-derived cells.[69] The authors were skeptical about the durability of regenerating cartilage from implanted chondrocytes. By coating the lumen of the construct with poly L-lactic-acid-co-caprolactone, which delays degradation of collagen, they were able to promote migration of the host's epithelium onto the collagen layer.[70]

In 2008, Jungebluth et al treated a patient for end-stage bronchomalacia by means of a decellularized donor trachea. (Fig. 6.2) Short-term incubation was performed with autologous chondrocytes differentiated from bone-marrow derived