

Feature

Therapy Focus: Wound Care

The niche market of wound care is occupied by a group of around 50 speciality biopharmaceutical companies with proprietary technologies that address a number of therapeutic areas. Wound care is a tremendously diverse market – from plasters and bandages to autologous skin replacement – so that within individual wound care approaches there are relatively few competitors. The Text Box gives a breakdown of the types of therapies that are used to treat chronic wounds, including products described in more detail in this article. In 40% of cases current standard therapies are ineffective in wound healing, and therefore this article will highlight some of the emerging therapies and products being developed to address this unmet clinical need.

The Wound Care Market

The need for effective wound care can arise from surgical interventions, including those in the fields of orthopaedic, cosmetic, vascular and endoscopic surgery, and from burns and skin ulcers, which are often symptomatic of an underlying pathology, such as infection, cancer, venous stasis, diabetes, amyloidosis and hypertension. The three most common types of chronic wounds are diabetic foot ulcers, venous leg ulcers and pressure ulcers. It is estimated that in the US 3 million patients suffer from chronic wounds.

According to the **Business Communication Company** the market for advanced wound care is growing at 10% per annum, and is estimated to reach US\$2.8 B by 2008, with the chronic wound market accounting for the largest portion of revenues. With the advent of new technologies and discoveries about the basic science of wound healing, carefully designed products are now entering the market and challenging the traditional and impregnated gauze markets which currently hold a majority share.

Novel Therapeutic Approaches

The first bio-engineered skin to receive US FDA approval was Apligraf®, which was registered for the treatment of venous leg ulcers in May 1998. This living cell-based therapy is indicated for the treatment of venous leg ulcers and diabetic foot ulcers. Apligraf is made of natural proteins and living human skin cells. The lower dermal layer is formed by human fibroblasts, which organise the structural protein provided and produce additional matrix proteins. The upper epidermal layer is formed by prompting human keratinocytes first to multiply and then to differentiate to replicate the architecture of the human epidermis. Unlike human skin, Apligraf does not contain Langerhans cells, melanocytes, macrophages or lymphocytes, or structures such as blood vessels, hair follicles and sweat glands. Developed by **Organogenesis**, the potential of this therapy was recognised by **Novartis**, which licensed the worldwide rights to the product in 1996, when it was awaiting approval by the FDA for the treatment of venous leg ulcers (Deal no. 02470); it was registered for this indication in June 2000. In September 2002, Organogenesis filed a voluntary petition for reorganisation under Chapter 11 of the US Bankruptcy Code. Before the Chapter 11 filing, Organogenesis terminated its agreement with Novartis, and reacquired the rights to Apligraf. In

Classification of Wound Care Therapeutics

Dressings	Plasters, compression bandages and synthetic dressings
Wound closure products	Sutures (Contour Threads™), staples and clips
Interventional wound healing	Electrical stimulation, oxygen therapies, vacuum-assisted therapies, low intensity/low frequency ultrasound through a mist
Moist dressings	Alginate (FlamineI®), films, foams
Topical antimicrobials	REP8839
Emerging Therapies	Skin substitutes (Apligraf®, PermaDerm™), growth factors (thymosin beta-4), gene therapy and debriding products (LarvaE BioFOAM)

June 2003 **PDI** entered into an agreement with Organogenesis in which PDI's Medical Devices & Diagnostics unit (PDI MD&D) was to provide sales, marketing and clinical support for Apligraf (Deal no. 13073). A restructured Organogenesis emerged from Chapter 11 in September 2003, and is continuing to manufacture and supply Apligraf for patients with venous leg and diabetic foot ulcers.

Angiogenesis – the formation of new blood vessels – is necessary for wound repair since the new vessels provide nutrients to support the active cells, promote granulation and tissue formation, and facilitate the clearance of debris. It is well documented that angiogenic factors are present in wound fluid and promote repair, while antiangiogenic factors inhibit repair. An interesting novel therapy for chronic wounds is a synthetic version of thymosin beta-4 (TB4), a peptide found in the body that plays an essential role in healing, regeneration and remodelling of injured or damaged tissue. Currently, thymosin is in Phase II clinical trials for decubitus ulcer (in the US) and for wounds (in both the US and Europe). Studies at the **US NIH** have shown that TB4 stimulates angiogenesis and is effective in rapidly healing injured tissues in rodents and other mammals. This promising product, which was discovered at the NIH, was licensed to **RegeneRx Biopharmaceuticals** in February 2001 (Deal no. 07478), and RegenRx subsequently sublicensed its European rights to **Defiante Farmaceutica** (of **sigma-tau Group**) in January 2004 (Deal no. 15325).

A second product whose mechanism of action is to enhance endogenous wound healing by promoting angiogenesis is **Athenagen's** small molecule agonist ATG 002, which targets the nicotinic acetylcholine receptor for the treatment of diabetic foot ulcers. In June 2006 Athenagen filed an IND with the US FDA and is now ready to initiate Phase I/II trials. In the future Athenagen will look to partner this topical compound, as it has expressed its intention to retain its primary focus on the therapeutic areas of

CNS and ophthalmology. The promise of using small molecules to stimulate angiogenesis is their relative resistance to tissue proteases and their ability to penetrate the surface of the wound.

A secondary factor that prevents wound healing is infection, and topical antimicrobials have often been applied to treat skin infections, and thereby enhance healing. Novel compounds in early-stage development include REP8839, part of an antibacterial programme licensed to **Replidyne** by **GlaxoSmithKline** (GSK) in June 2003 (Deal 13059). In return for worldwide rights to this programme GSK received an equity position in Replidyne. The programme includes multiple series of advanced leads and related IP, and in July 2006 produced its first Phase I clinical candidate, REP8839, a topical anti-infective that is being developed for the treatment of skin and wound infections, and for the prevention of *Staphylococcus aureus* infections.

One of the perhaps more unconventional treatments for the treatment of wounds is the use of sterile maggots (usually of the greenbottle fly *Lucilia sericata*). Small-scale trials have shown these maggots to be beneficial in the treatment of venous, arterial and pressure ulcers through digestion of the necrotic material in the wound without damage to the surrounding healthy tissue. A company furthering this research is UK-based **ZooBiotic**, which has been selectively breeding maggots for improved viability and enhanced ability to digest dead tissue. In a second product, free-range maggots are used in combination with an absorbent hydrophilic polyurethane foam – LarvaE BioFOAM. The foam appears to stimulate larval activity by assisting with exudate management. Careful assessment of the wound is required to choose whether free larvae alone or LarvaE BioFOAM should be used: despite the practical and aesthetic advantages of the BioFOAM, patients who have wounds with cavities or areas of undermining should use larvae alone.

Consolidation in the Market

With speciality pharmas generally having only one or two products in a niche indication and requiring a sales force that can reach their desired client base, it is more economical for a sales force to sell a portfolio of complementary products, and this factor has driven the trend of consolidation that has been seen in the fragmented wound care market. Since 2000, some 18 business acquisitions/mergers/divestments have been undertaken, and these account for some 13% of the total wound care deals that have occurred (*Figure 1*); key examples are outlined below.

In February 2006, **Cambrex Bio Science Walkersville**, a subsidiary of **Cambrex**, entered into a purchase agreement for all of the stock of **Cutanogen**, a privately held biotechnology company that is focused on products used to treat patients with severe burns (Deal no. 23313). The purchase price consisted of US\$1.5 M to be fully paid at closing, with additional payments of up to US\$4.8 M subject to the achievement of certain regulatory and commercial milestones. Cutanogen's lead product is PermaDerm™ cultured skin, which combines autologous epidermal and dermal layers of the skin in a multilayered product that is pliable and grows with the patient, a particular advantage when the burn patient is a child. Cambrex anticipates applying for a Humanitarian Device Exemption (HDE) with the FDA by mid-2006, and intends to begin a pivotal trial for PermaDerm cultured skin by the end of 2006. The trial is estimated to take approximately 15 months, and upon completion of the analysis of the pivotal

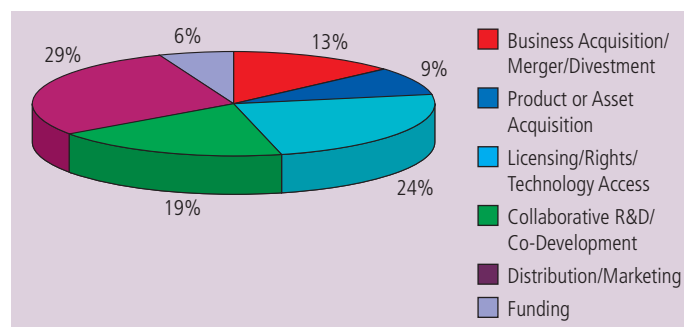


Figure 1 – Deal making patterns in the wound care product industry (Source: PharmaDeals® Agreements).

trial data, Cambrex expects to submit the results to the FDA in its application for Pre-Market Approval (PMA) for commercial sale.

Nearly 4 months later, in May 2006, **Angiotech Pharmaceuticals** entered into a definitive agreement to acquire privately held **Quill Medical**, a provider of minimally invasive aesthetic surgery and wound closure technology, for US\$40 M in cash plus certain future contingent payments based on product revenues (Deal no. 24373). Through this transaction, Angiotech will acquire all of Quill's technology and IP, including the Contour Threads™ product line of non-absorbable barbed sutures.

In December 2004 **IsoTis OrthoBiologics** divested its wound management unit, **EpiSource**, to **DFB Pharmaceuticals** for an undisclosed amount (Deal no. 18764). DFB is a US-based company, which through its subsidiary **Healthpoint**, is concerned with advanced wound care, dermatology and surgical products. Healthpoint subsequently went on to purchase **BioSpecifics Technologies'** topical collagenase business in March 2006 (Deal no. 23635). As part of the agreement, Healthpoint's affiliate (DFB) will assume ownership and operation of BioSpecifics' manufacturing facility in Curaçao, and of certain other assets in Lynbrook, New York that are owned by BioSpecifics' affiliate, **Advance Biofactures**. Deal terms involve an upfront cash payment of US\$8 M to BioSpecifics on signing for the assets and an additional payment for future services to be provided by Advance Biofactures. The deal terms also include the potential for BioSpecifics to benefit from an earn-out based on sales.

The UK-based company **Ark Therapeutics Group** provides an example of a company that is seeking to strengthen its wound care range through both in-licensing and in-house development of products. Ark launched its leg and foot ulcer care device **Kerraboot®** in the UK in May 2004. The device is designed to allow free drainage of chronic wound exudate away from the wound bed and to lock it away into the super absorbent pad at the base of Kerraboot, while at the same time creating and maintaining an optimum moist healing environment around the wound surface. In June 2006 Ark strengthened its portfolio by in-licensing **Flen Pharma's** **Flaminal®** wound care gel for the UK (Deal no. 24573). Flaminal is a non-cytotoxic alginate gel with antimicrobial properties that uses an enzyme system, and is indicated for wounds that show delayed healing as a result of a local infection or high bacterial load.

All in all, the future market for wound care looks set to continue to grow, and dynamic speciality pharmaceutical companies with innovative approaches seem likely to be able to capture a good market share.