Wound Healing Foresighting Report

Technology & Markets
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Life Sciences SCOTLAND

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Executive Summary

- The advanced wound management market was worth nearly $4B in 2007 and forecast to reach $6B by 2010. This market targets the hard-to-heal and chronic wounds such as diabetic foot ulcers that are growing in prevalence. These wounds can take years to heal. There is a need for new, more clinically efficacious products to accelerate the time to heal and increase the number of wounds healed.
- However, this market has been viewed with scepticism for a number of years despite the clear market need. Investor interest in this area was significantly eroded following the disappointing sales of several advanced therapies and the failure of a number of wound healing agents. The recent success of Kinetic Concept's VAC system has reignited interest, however. Kinetic Concepts has revolutionised the sector, pulling in over a billion dollars in revenue. VAC's success has served to demonstrate the huge market potential for effective approaches.
- There is a number of emerging technologies that could form the basis of future advanced wound care products. These relate to innovations around intelligent skin substitutes, biologics, gene therapies, stem cells, alternative physical therapies and infection control. Recent research directed towards understanding the aetiology of chronic wounds has also highlighted the potential new therapeutic and diagnostic opportunities relating to biofilms, nitric oxide and proteases. There is also scope for innovation around the treatment of chronic wound pain. This has the potential to become a a new therapeutic class of dressings and so may be a significant market opportunity.
- The advanced wound management market is, however, challenging. Companies developing advanced wound therapies must balance the need to deliver typically high-technology products that stimulate the healing process with the budgetary healthcare pressures. Indeed, there is mounting pressure for companies to demonstrate the cost effectiveness as well as efficacy of their products. This, together with the increased regulatory requirements of the more advanced products, significantly impacts development costs.
- In conclusion, ITI believe that advanced wound management is a sizeable and growing market with a clear need for new and improved products. There is a number of emerging technologies and new applications. However, the market potential of these opportunities must be weighed against the increasingly high development costs of such products and the price sensitivity of the industry.

Scope

- The goal of any new wound healing treatment is to accelerate closure of the wound and to avoid infection and other complications in a cost-effective manner.
- The various wound types are treated in a variety of settings. This report concentrates on the more technically challenging and hence potentially more commercially valuable wound types. These are the difficult-to-heal and chronic wounds of the skin that require advanced therapies to assist healing by secondary intention.
- The foresighting focus is therefore on the **advanced wound management market**, which addresses this need.
- Other segments of the general wound care market, such as technologies addressing minor, self-treated wounds or acute wounds such as traumatic or surgical wounds that heal by primary intention (e.g. suturing), are outside the scope of the present analysis.
- Opportunities in wound care diagnostics are not discussed as these were assessed during a recent foresighting activity by ITI Techmedia.

Contents

- Dynamics
- Drivers
- Restraints
- Challenges
- Players

- Acute
- Chronic
- Infected

- Moist dressings
- Antimicrobial
- Advanced therapies
- Tissue engineering
- Physical therapies

- Infection control
- Pharmaceuticals
- Tissue engineering
- Physical therapies
- Pain management
- New concepts

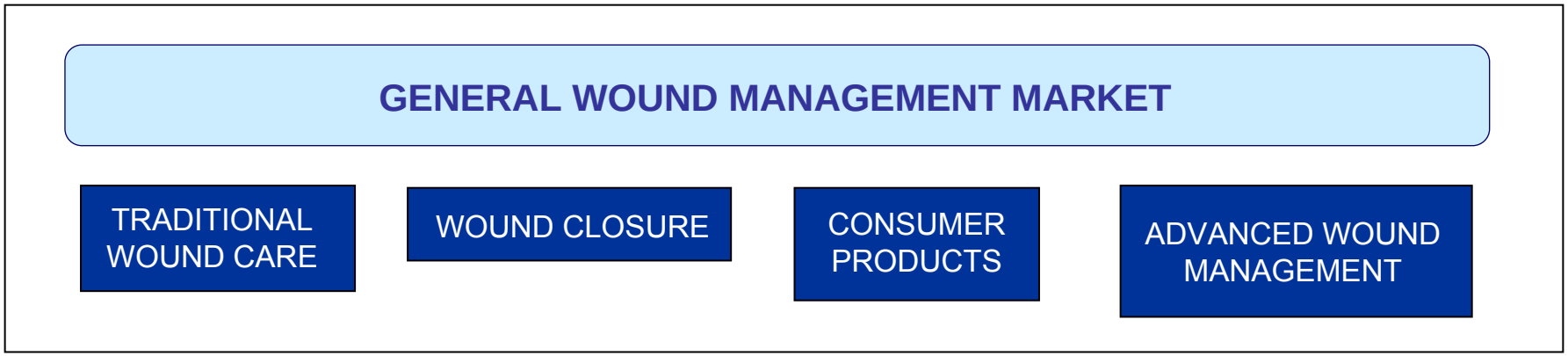
Advanced Wound Management Market

Introduction

- The advanced wound management market has been viewed with much scepticism by venture capitalists (VCs) for a number of years. The failure of a series of wound healing agents, combined with the disappointing sales for the few products that were approved, significantly eroded interest in this sector.
- The success of Kinetic Concept's Vacuum Assisted Closure (VAC) system has recently re-ignited interest in this sector. The company has revolutionised the advanced wound care market, pulling in over a billion dollars in revenue from a single product.
- The success of VAC has served to demonstrate the huge market potential for effective approaches. The knowledge that the need for such products will only expand as the population ages and the number of individuals with diabetes (and therefore at risk from diabetic ulcers) rises has further increased the attractiveness of this market to investors.
- The current advanced wound management market can be segmented in a number of ways. This report describes the market first in terms of product category and then by wound type.

Market Segmentation by Product Category

General Wound Management Market



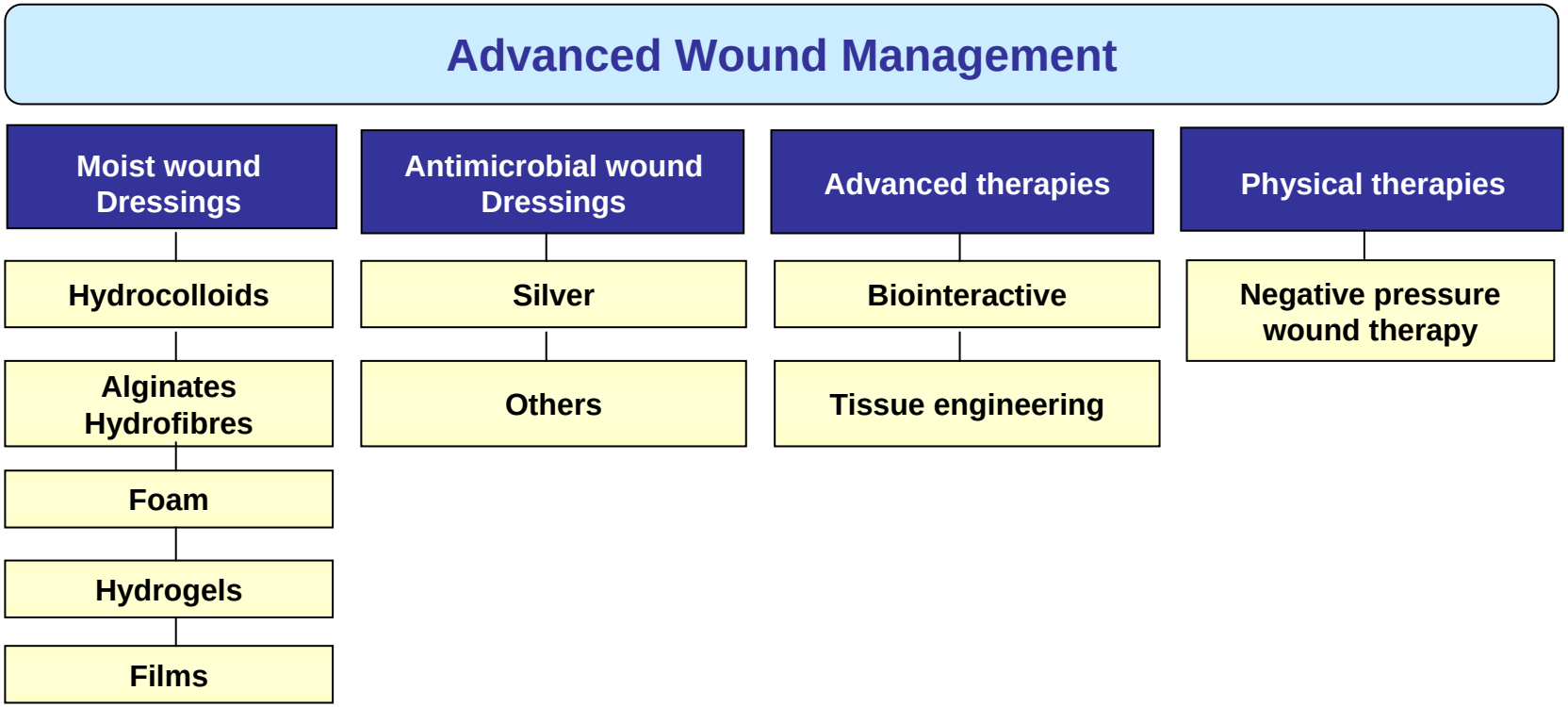
- Advanced wound management (AWM) is one category in the general wound management market.
- Traditional wound care includes products such as tape and gauze; a sizeable market remains for these products in less socio-economically developed countries.
- Wound closure includes long-established devices such as sutures and staples, as well as more recent technologies such as tissue sealants and glues.
- The consumer wound care sector largely covers dressings used in a first-aid context or home setting.
- MedMarket reports the total wound management market to be worth $14B in 2007 and forecast 7% growth (CAGR 2007–2016). This growth is to be generated predominantly through growth in the advanced wound management market.

AWM Market Overview

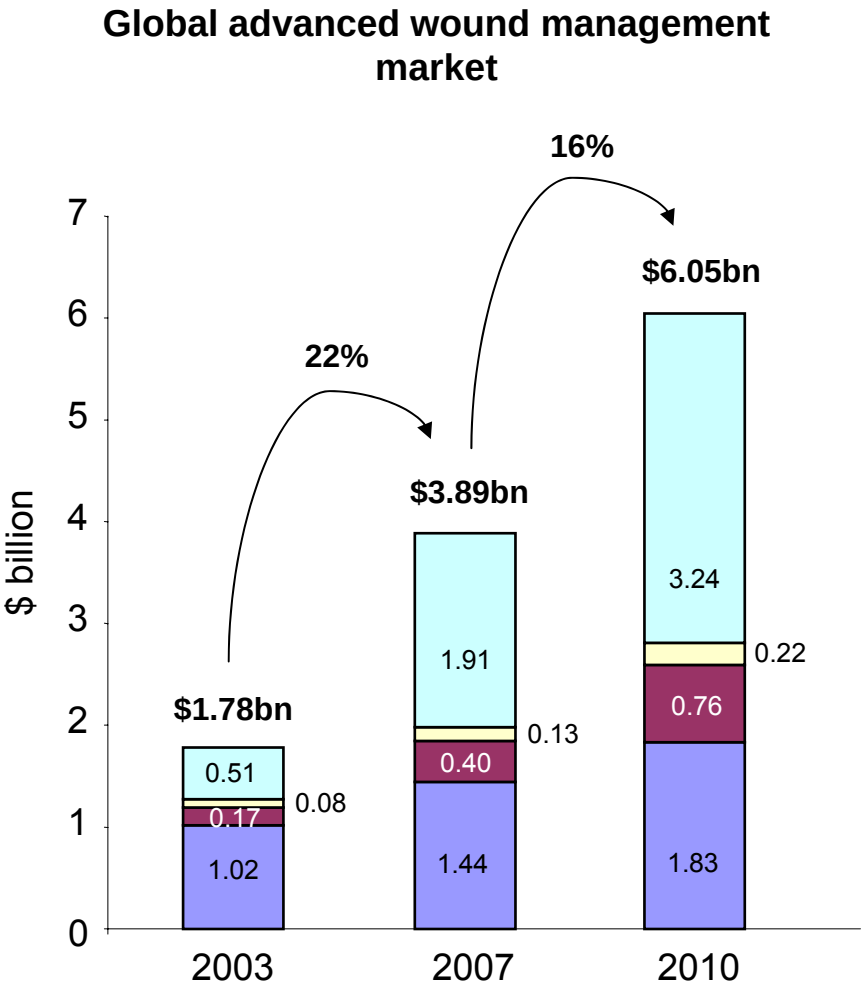
- Advanced wound healing products were first developed in the 1970s with the advent of the 'moist wound healing' concept. This demonstrated that healing was accelerated when the wound was kept moist rather than allowed to dry. Prior to this, the most common treatment for wounds was tape and gauze.
- This sector has grown over the past 30 years. The moist wound concept has stimulated the development of a wide range of 'advanced' dressings, all of which are aimed at maintaining the optimum moisture balance within the wound using different material technologies. The majority of products in this group have now reached commodity status where competition is largely on the basis of price.
- Only nominal growth of the established advanced wound healing technologies is forecast, as this area is now reaching maturity. However, there are still some niches where dressing development is still the focus of attention, e.g. for malodorous wounds in difficult-to-dress locations such as fungating carcinomas of the breast.
- The advanced wound-care market has recently seen the development of newer technologies, some of which have reached the market. There is greater scope for innovation and value generation in development of such products.

ESTABLISHED TECHNOLOGIES	NEWER TECHNOLOGIES TO THE MARKET
Films	Negative pressure wound therapy
Hydrocolloids	growth factors
Alginates	Tissue engineering (skin substitutes)
Hydrogels	
Non-adherent dressings	
Cleansers and debriding agents	
Silver dressings	

AWM Market Segmentation



Global AWM Market

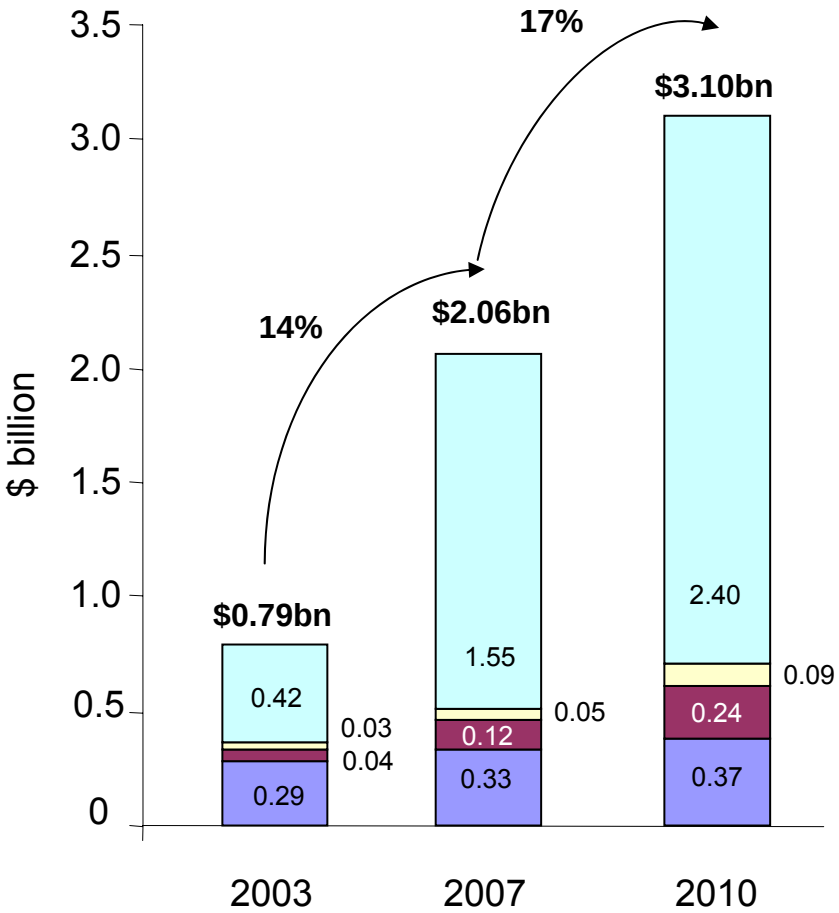


- The fastest-growing segments of the advanced wound management market are the new therapies within the more mature aspects of the market, notably moist wound dressings. These are due to experience more nominal growth.

CAGR	2003–7	2007–10
Negative pressure therapy	39%	19%
Advanced therapy	13%	18%
Antimicrobial dressings	24%	24%
Moist wound dressings	9%	8%

Market by Region: US

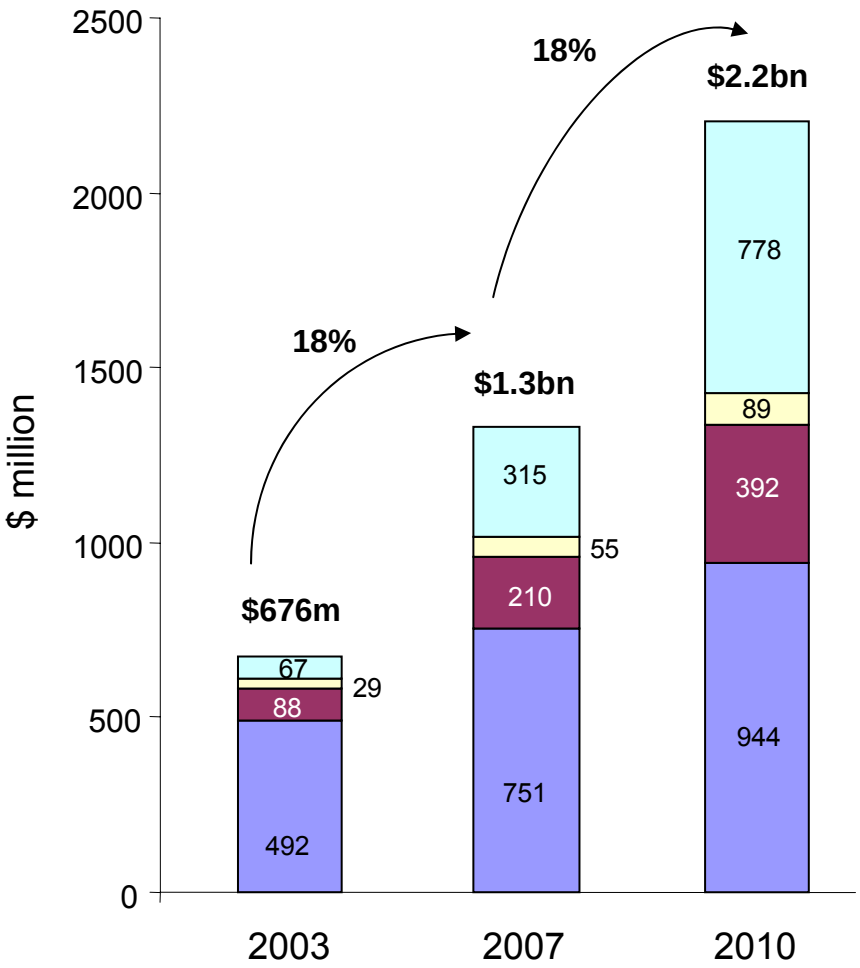
US advanced wound management market



CAGR	2003–7	2007–10
Negative pressure therapy	38%	16%
Advanced therapy	17%	17%
Antimicrobial dressings	28%	25%
Moist wound dressings	4%	4%

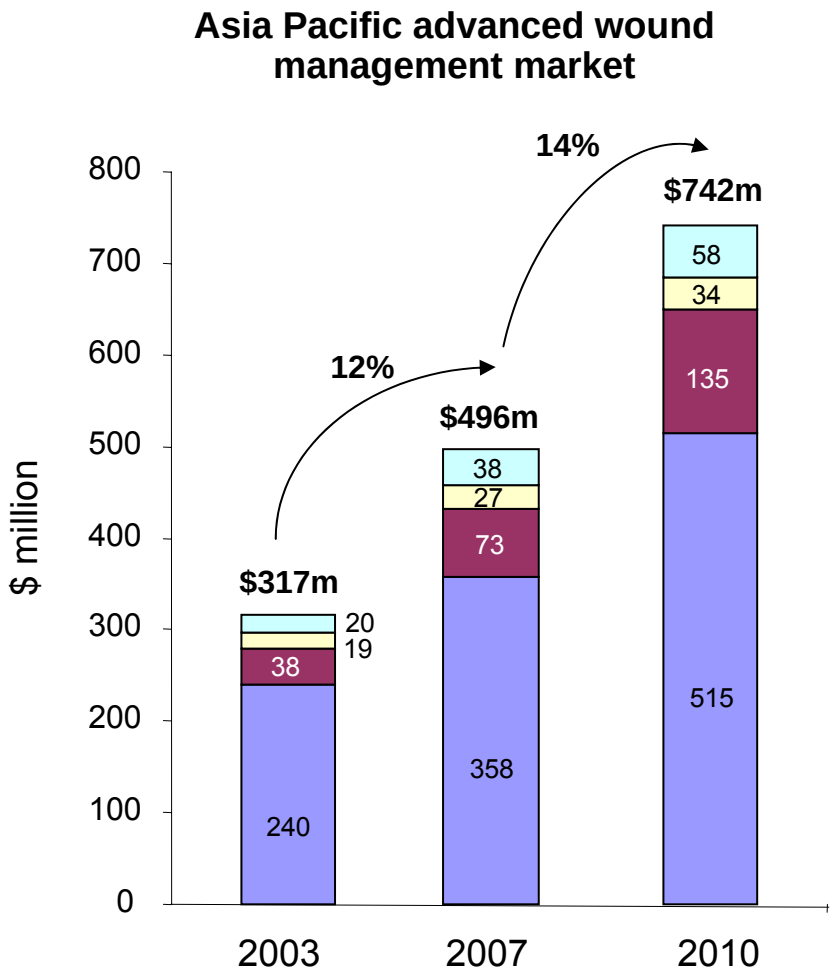
Market by Region: Europe

European advanced wound management market



CAGR	2003–7	2007–11
Negative pressure therapy	47%	35%
Advanced therapy	17%	17%
Antimicrobial dressings	24%	23%
Moist wound dressings	11%	8%

Market by Region: Asia Pacific



- The Asia Pacific markets for advanced wound management are emerging. Although wound care needs are growing rapidly in this market, advanced wound management is expanding at a lower rate due to the limited financial infrastructure and the dominance of less expensive traditional dressings.

CAGR	2003–7	2007–11
Negative pressure therapy	17%	15%
Advanced therapy	8%	8%
Antimicrobial dressings	18%	23%
Moist wound dressings	10%	13%

Market Drivers

1. Favourable trends in demographics expand potential market size

- Demographics such as the increasing ageing population and the rise in both obesity and diabetes will lead to an increase in the number of chronic wounds.

2. Need for improved products

- Wound healing is currently imperfect; there is no guarantee that a particular treatment will heal a particular wound and so there is continuing demand for improved products.
- There also appears to be scope for new product introduction. Smith & Nephew, for example, reported that 29% of its revenues in Q3 2007 were from 'new products', although a significant proportion of this can be accounted for by line extensions and acquisitions.

3. Drive for infection control encourages use of antimicrobial products

- Increased infection rates and the rise in MRSA infection control will drive the market for antimicrobial products.

4. Demonstrated and recorded clinical efficacy of products stimulate further use

- Good clinical outcomes will increase product acceptance and willingness to use among clinicians. Patients are also becoming better informed and requesting more advanced therapies. The increasing risk of litigation for suboptimal treatment could increase use of the more effective yet more expensive products.

Restraints

1. Increasing pressures on healthcare budgets and the drive for reductions in product cost

- Cuts in healthcare expenditure have led to a general lowering of reimbursement levels; products in this market are experiencing significant price pressures. Players are striving to counter budgetary pressures by demonstrating the overall cost effectiveness of new advanced wound care products. However, payers are still placing considerable emphasis on 'price per piece' rather than 'total cost'.
- Many advanced products, such as skin substitutes, are significantly more expensive than alternative therapies. Publicly funded healthcare organisations sometimes find these costs difficult to absorb despite strong cost-effectiveness claims. Companies are striving to lower manufacturing and product design costs to enhance the cost effectiveness of these products. As unit volume increases, the costs of products might also decline to a point where they can demonstrate cost effectiveness in the treatment of other wound types.

2. R&D costs restricts market development

- The high costs of emerging technologies can be partly attributed to: (i) the increased clinical and economic evidence required to ensure adoption, with its knock-on impact on development timescales and (ii) increased regulatory burdens as devices incorporate biologic components.

3. Improved wound prevention might dampen market expansion

- Awareness regarding wound prevention is growing. This could help stem the rise in diabetic ulcers and pressure sores and so dampen market expansion.

Restraints … continued

4. Lack of basic research into wound healing processes

- Wound healing is a complex process. Although our understanding of the wound healing process has undoubtedly improved, research is still required if we are to fully understand the molecular and biochemical pathways involved. The information available to guide selection of the most appropriate biochemical targets to influence wound healing is limited, and this shortage of information is hindering the effective development of novel therapies. As a result, some of the products developed are presumably of suboptimal efficacy.

5. High number of competitors and lack of awareness of new technologies

- There is a relatively large number of participants in the advanced wound management market compared to other medical device markets. This facilitates the market education process, which is important as conservatism and lack of awareness have been reported to significantly inhibit adoption of new technologies in this sector. However, it means that a number of companies have relatively similar product ranges, which is likely to drive down prices further or lead to further market consolidation, and makes product differentiation challenging.

Challenges

1. The complexity of chronic wounds

- The complexity of the wound healing process means that the slow-to-heal wounds are unlikely to be addressed using a single modality. This confines products to dealing with part of the problem, and hence to achieving only part of the reward.

2. Regulatory constraints

- The regulatory environment and reimbursement frameworks for more advanced wound healing therapies are complex.
- A wide range of regulatory approval conditions are applied to wound management products. Wound care products generally fall within the Class I and Class II device categories. However, advanced wound management products are increasingly being designated as Class III devices due to their biologic components. Gaining approval for a Class III medical device demands almost the same level of evidence as for a pharmaceutical product. The integration of new pharmaceutical and biological agents in wound healing increases the regulatory burden and increases development costs.
- Development of technologies with a lighter regulatory burden has allowed some products to be brought to market with little supporting data.

3. Big player dominance

- The trend towards bulk central purchasing by healthcare providers limits scope for innovative products and increases the dominance of big players, who can provide a broad product portfolio. However, KCI has demonstrated that it is still possible for a single-product company to significantly impact the market.

Challenges … continued

4. Product differentiation and marketing

- The clinical community is currently overloaded with choice. An ability to differentiate technology from the myriad of others available will be important. Sales and marketing is a key capability within this market.
- The proliferation of different wound care products and strategies has also led to confusion and uncertainty over best practice. The World Union of Wound Healing Societies has recently released consensus documents in a bid to standardise practices.

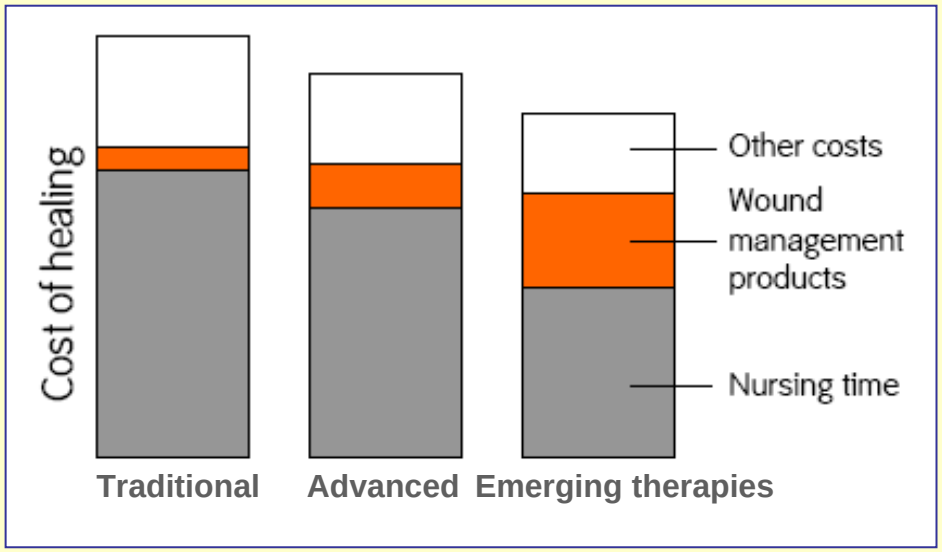
5. Demonstrating efficacy

- Clinical efficacy is often difficult to demonstrate because subjects in the control group tend to show improvements as the standard of care they receive improves once enrolled on the clinical trial. Trial design must be optimised to counter this issue. For example, patients could be screened and placed on a standard care programme before starting the trial.
- The time and cost required to demonstrate clinical efficacy is also significant. However, it should be noted that, depending on its regulatory classification, it still remains possible to market a product with limited clinical evidence.
- There is also a need for new and improved models. 2D in-vitro cell culture models struggle to reflect the complexity of the wound bed. In-vivo rodent and rabbit models are also limited because of key differences between the wound healing processes of these animals and humans. The animal models: (i) heal by contraction rather than by re-epithelialisation, as observed in humans; (ii) have many hair follicles; and (iii) have looser skin than humans. As a result, the porcine model is generally used, although some researchers are now promoting the use of human skin equivalents.

Challenges … continued

6. Proving cost effectiveness

- With the demand for greater efficiency across the healthcare system, there will be an increased demand for proving cost effectiveness prior to reimbursement.



Key outcome measures

- % patients with complete healing or in whom therapy has advanced the wound to a stage of healing
- Time to complete healing

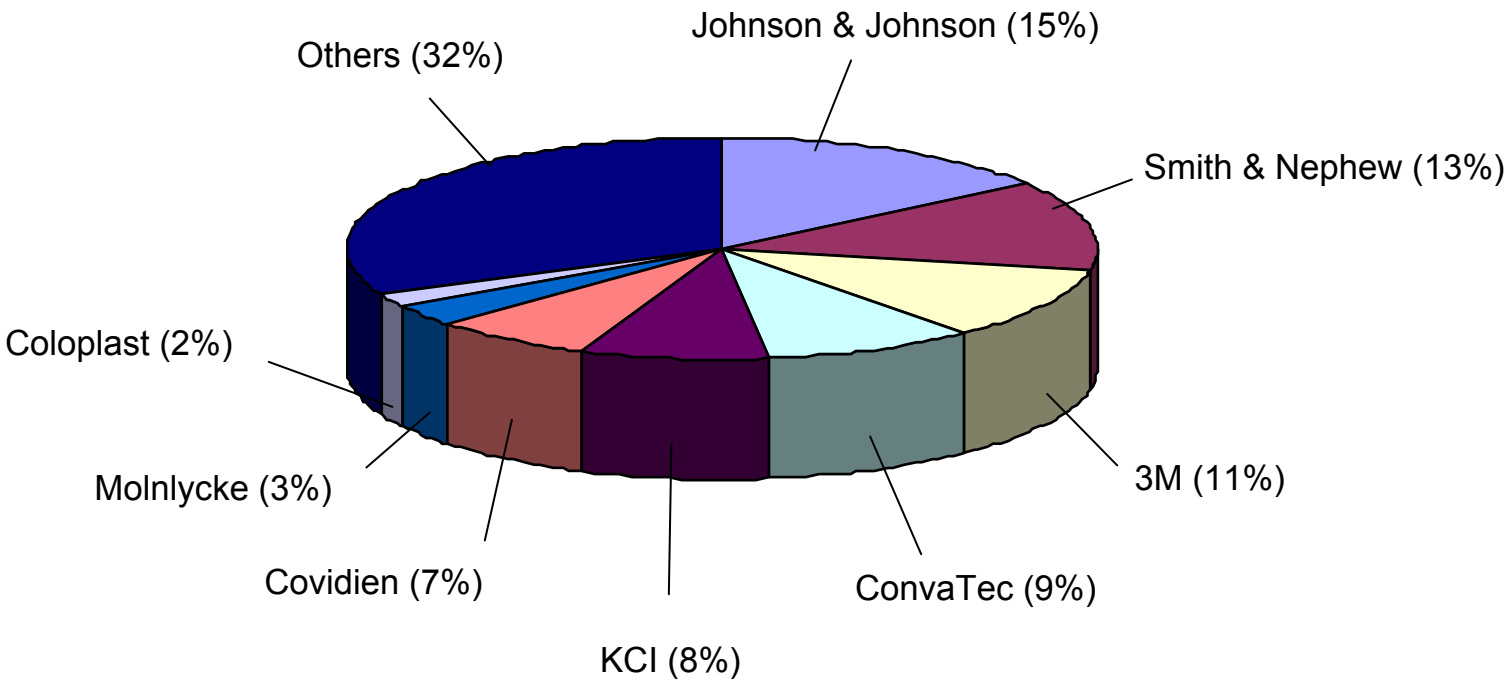
Other clinically meaningful outcomes

- Change in wound size
- Enhanced standard of daily life
- Pain reduction
- Reduced infections
- Need for debridement
- Improved cosmesis

- Higher revenues can be achieved from the sale of advanced wound management products if they reduce the overall cost of wound treatment, e.g. by reducing treatment time, dressing changes. It is generally easier to demonstrate cost effectiveness with diabetic foot ulcers, where amputation is relatively common.
- The decision-making relating to the purchase of new wound care products is complex and requires the involvement of a number of stakeholders. Although clinicians play a leading role in the introduction of new products, they are concerned primarily with clinical effectiveness. Data supporting the cost effectiveness of products are essential to convince the budget holders that they should buy.

Players in General Wound Management

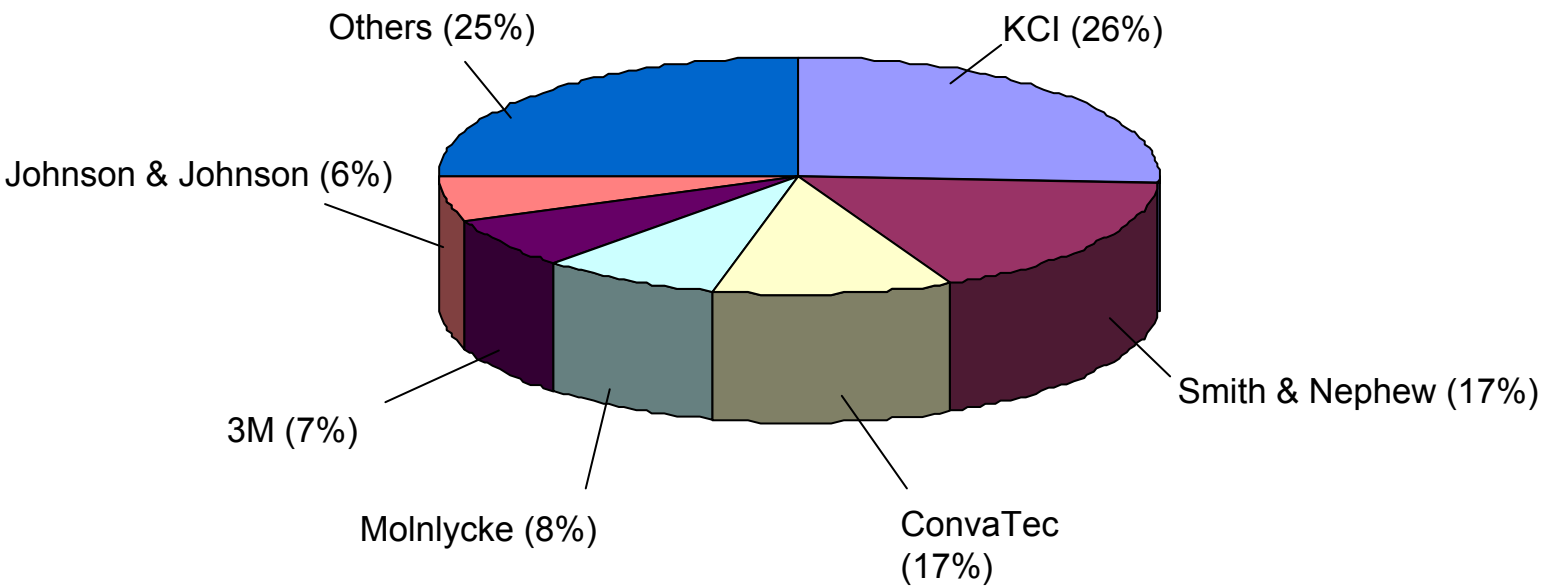
General wound management market: Company market share by revenues (worldwide)



- The US is the largest national market for wound care products with 38% of world sales. European countries represent 25% of the global market with Japan accounting for 13%.
- Bristol-Myers Squibb sold ConvaTec to Nordic Capital Fund and Avista Capital Partners for $4.1bn in May 2008.

Players in Advanced Wound Management

Advanced wound management market: Company market share by revenues (worldwide)



- The US share of the advanced wound management market is believed to be 41%, with the major European countries (UK, Italy, France, Germany) accounting for 23% of the market.
- It is clear that different countries are at different stages of market development. The UK, for example, is very advanced, whereas other EU countries (e.g. Spain and Italy) lag significantly behind.

Market Segmentation by Wound Type

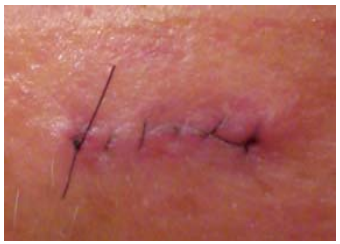
Market Segmentation by Wound Type

Advanced wound management

- **Acute wounds**
  - Surgical
  - Traumatic
- **Burns**
- **Chronic wounds**
  - Pressure ulcers
  - Venous leg ulcers
  - Arterial ulcers
  - Diabetic foot ulcers
- **Others**
  - Carcinomas
  - Melanomas
  - Amputations
  - Radiation injury
  - Frostbite, etc.

Infected wounds

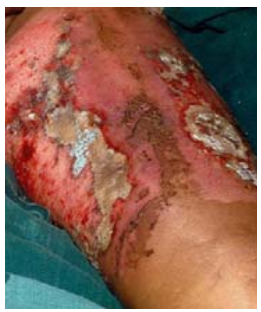
Acute Wounds & Burns



ACUTE WOUNDS

- These are the most common type of wound. There are approximately 100 million surgical incisions per annum and approximately 50 million traumatic wounds, including lacerations, caused by accidental injury. This market segment is well served by commodity products such as sutures, staples and a large variety of dressings.
- Most of these wounds heal uneventfully by primary intention following surgical closure and generally require only a dressing or bandage to provide protection, rather than to have an active influence on healing. However, surgical or traumatic wounds involving substantial tissue loss may be left to heal by secondary intention, and so some acute wounds will require advanced wound management therapies. KCI's product, VAC, has been particularly successful in treating traumatic wounds and non-resolving surgical wounds.

- Although largest in terms of wound numbers, this wound type is the least interesting commercially due to the commodity nature of the majority of products used, as most heal uneventfully. The reduction in severity and size of surgical wounds noted with the move towards minimally invasive surgery will also limit the need for advanced wound care products for this wound type.



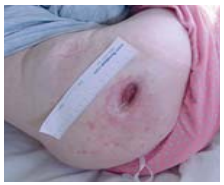
BURNS

- Approximately 6 million minor burns are treated medically each year, usually with antimicrobials and dressings to maintain hydration and protect the wound. Hospitalised burn wounds are rarer (approximately 100,000 in the US and 10,000 in the UK). These require more advanced and expensive care, which may include tissue grafting and tissue engineering, and so are appropriate candidates for treatment using advanced wound management therapies. However, these wounds represent a relatively small market segment in terms of volume.

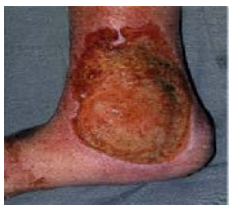
Chronic Wounds

CHRONIC WOUNDS

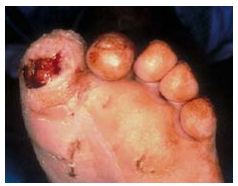
Chronic wounds include pressure ulcers, venous leg ulcers, arterial ulcers and diabetic foot ulcers. Such wounds may be treated in hospital (where they can be the cause of expensive extended stay) or in the community (at clinics or in the patient's home).



- **Pressure ulcers** are areas of local necrosis resulting from vascular insufficiency due to prolonged application of pressure to the tissues. These may occur in healthy adults if sufficient pressure is applied to close capillaries, although significantly lower pressures may lead to ulcer formation in an elderly patient.

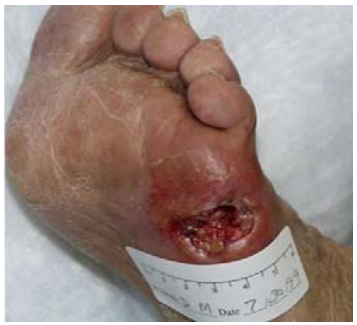


- **Venous leg ulcers** are a symptom of underlying venous hypertension or chronic venous insufficiency, and so treatment is required to counteract the underlying condition. Incidence increases with age. It is estimated that 2% of the population may experience this type of wound during their lifetime, with 60% of these wounds taking longer than 2 years to heal. Venous leg ulcers reportedly cost between $1042 and $2552 per patient to treat in the UK.



- **Arterial ulcers** are a direct result of inadequate tissue perfusion to the feet or legs due to complete or partial blockage of the arterial supply. There is little chance of healing an arterial ulcer until the blood supply to the area is re-established.

Chronic & Other Wounds



- **Diabetic foot ulcers** (DFU) are relatively common, with approximately 20% of all diabetic patients experiencing a foot ulcer in their lifetime. They are due mainly to peripheral neuropathy (both sensory and motor) and vascular disease coupled with an unrecognised repetitive minor trauma. Minor trauma such as ill-fitting shoes can go unrecognised due to loss of pain sensation and so leads to ulceration.
- Many of these patients will require amputation within the foot or above the ankle as a consequence of severe infection or peripheral ischaemia. Indeed, diabetes is the leading cause of non-traumatic lower extremity amputations in the US, with 12–24% of individuals with a foot ulcer requiring amputation.
- In the US, it is estimated that 5% of people with diabetes develop a DFU each year, with 1% requiring amputation. Even if the ulcer heals after successful wound management, recurrence occurs in 66% of patients and the amputation rate rises to 12%; the 5-year risk of needing a contralateral amputation is 50%.
- The estimated cost of treating a DFU in the US is up to $20,000, with a major limb amputation costing approximately $70,000. Recent estimates reveal that DFU and amputations alone cost the US healthcare system about $30bn per year, with lower extremity complications accounting for approximately 15–40% of the total cost of diabetes. The associated costs of amputation aids the cost–benefit argument for use of advanced wound management products to treat this wound type.

OTHER WOUNDS

- Wound management products are also used for a number of other conditions, including carcinomas, melanomas and other complicated skin cancers, which are all on the increase but are relatively small in number compared with the major chronic wound types described above.

Projected Market Growth by Wound Type

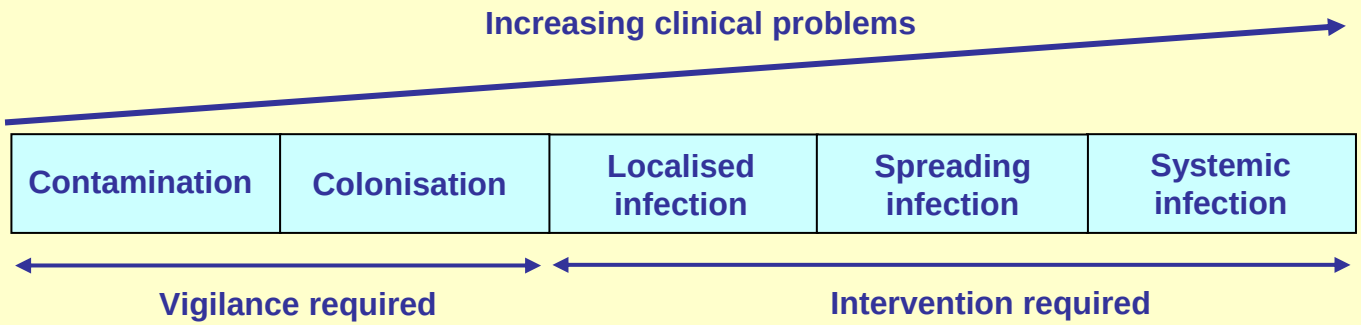
Wound type	Worldwide incidence (millions)	Healing time (days)	CAGR (2005–14)
Surgical wounds	96.7	14	3.1
Traumatic wounds	50	28	1.4
Lacerations	19.5	14	1.0
Burn wounds (out-patient)	3.5	21	1.0
Burn wounds (medically treated	6.2	21	1.0
Burn wounds (hospitalised)	0.2	50	1.1
Pressure ulcers	**6.6**	–	**6.2**
Venous ulcers	**9.7**	–	**6.4**
Diabetic ulcers	**10.0**	–	**9.4**
Amputations	0.2	–	0.9
Carcinomas	0.6	14	3.0
Melanoma	0.1	14	3.0
Complicated skin cancer	0.1	28	3.0

The predicted growth in the incidence of chronic wounds is largely due to demographic factors, such as increasing age of the population, increasing incidence of diabetes and lifestyle factors (e.g. the rise in obesity).

Wound Infection: A Costly Complication

- A significant feature of all wounds is the likelihood of pathological infection occurring.
- Treatment of wound infection is key in assisting the wound to heal. Indeed, it has been shown that high levels of bacteria inhibit every step of the healing process. Pathogenic microbes compete with the macrophages and fibroblasts in the wound bed for limited resources and can cause further necrosis, with microbial by-products resulting in unpleasant odours.

When to treat?

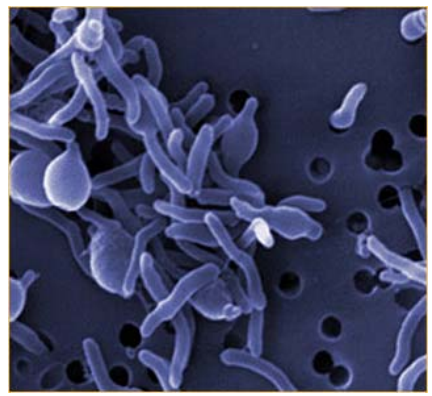


- **Contamination**: Bacteria do not increase in number or cause clinical problems.
- **Colonisation**: Bacteria multiply but wound tissues are not damaged.
- **Infection**: Bacteria multiply, healing is disrupted and wound tissues are damaged (local infection). Bacteria may produce problems nearby (spreading infection) or cause systemic illness (systemic infection). Localised infection is often characterised by the classic signs and symptoms of inflammation (pain, heat, swelling, redness, etc.). However, bacteria can stall healing in the absence of obvious indicators of inflammation, particularly in chronic wounds. This more subtle state of localised infection has been termed by some 'critical colonisation'.

Wound Infection

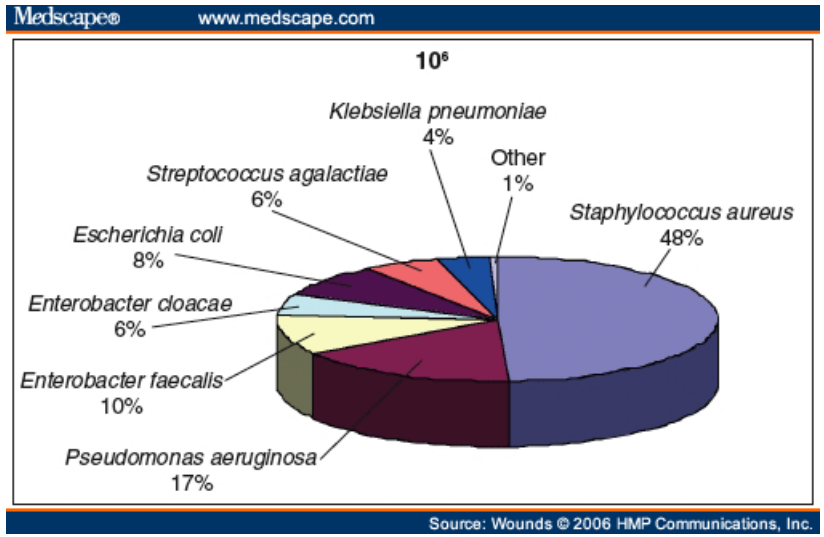
- All wounds tend to contain bacteria, although not always with a detrimental effect. Current data suggest that 50–70% of diabetic foot ulcers are colonised and contaminated; the percentage of diabetic foot ulcers believed to be pathologically infected ranges from 20 to 30%.
- Because of the difficulties associated with performing quantitative biopsies, visual inspection of wounds is commonly used to diagnose infection. However, initial visual assessment might indicate the need for microbiological analysis. Sampling techniques include swabbing, needle aspiration and biopsy, with wound swabbing most widely used. Venous leg ulcers are particularly problematic to diagnose visually as the characteristics of chronic venous disease closely mirror the cues (warmth, tenderness, erythema, swelling, foul odour, etc.) used by the clinician.

- The diagnosis of infection is made when the wound culture demonstrates bacterial counts in excess of 10^5 colony forming units per gram of tissue biopsy (with the exception of β-haemolytic streptococci, for which presence at any level indicates infection).
- Infection is not limited to chronic wounds. The average levels of infection of surgical wounds are in the order of 7–10%, depending on the procedure. These infections can be prevented by appropriate cleanliness, surgical discipline and skill, wound care therapy and antibiotic prophylaxis.
- Infections usually lead to more extensive wound care time, the use of more expensive products and drugs, significantly increased therapist time, and increased morbidity and rehabilitation time. If untreated, wound infection can lead to sepsis and eventually death.



Wound Infection

- Recent studies have shown the majority of venous leg ulcer infections to be monomicrobial, with bacterial prevalence shown below.



- Polymicrobial infections predominate in severe diabetic foot infections and include a variety of aerobic Gram-positive cocci, Gram-negative rods and anaerobes.
- The potential for bacteria to produce harmful effects is influenced by the ability of the patient's immune system to combat the bacteria, the number of bacteria introduced and type of bacteria.
- Effective management of wound infection requires optimisation of host response, for example through improvement in glycaemic control, as well as reducing the number of micro-organisms through debridement, cleansing and antimicrobial therapy.
- It should also be noted that other micro-organisms, such as fungi or viruses, can also cause wound infection, particularly in patients with impaired immune defences.

Chronic & Infected Wounds: An Opportunity?

Time-to-heal

- Chronic wounds take considerably longer to heal than other wounds. The time-to-heal is highly variable, with the majority of venous leg ulcers, for example, taking longer than 2 years to heal. This is partly due to the variation in care; many chronic wounds are believed to be treated suboptimally. The patient's health can also influence healing times, as can certain prescribed drugs. Chronic wounds require advanced wound management products and optimal care to address the underlying defect that has led to the chronic wound and so stimulate healing.

Growing prevalence

- The extended time-to-heal of these wounds, coupled with their growing prevalence due to the rise in diabetes and an ageing population, has resulted in a significant growth in the patient pool requiring treatment.

Infection

- Chronic wounds are likely to become infected. This is a costly complication because it slows the healing process and leads to extended treatment times and costs.

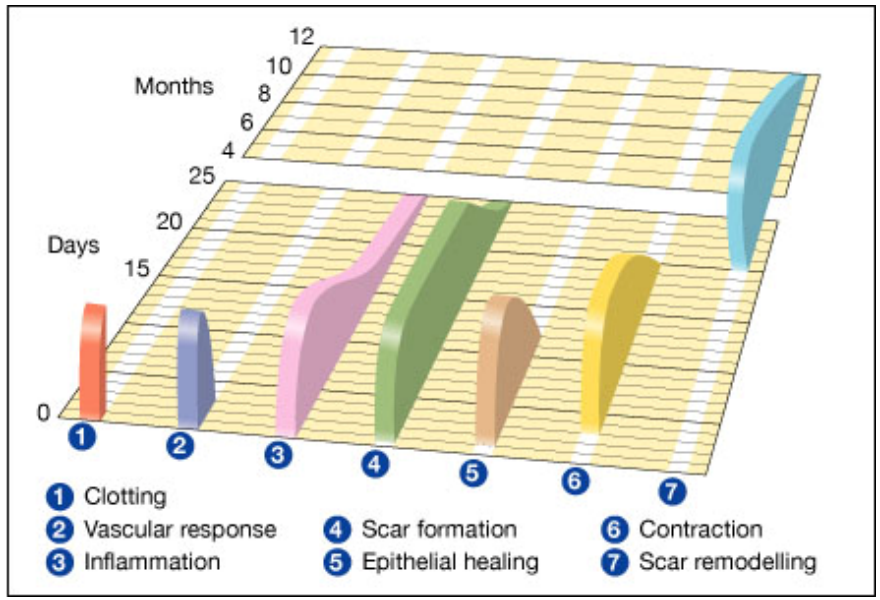
Opportunity?

- The growing market size, the lengthy time-to-heal and the need for advanced technologies to stimulate healing makes chronic wounds, particularly diabetic foot ulcers, an attractive market.
- The high incidence of infection and the significant barrier it raises to wound healing highlights the opportunities in this space.
- According to Piribo, sales of products used to treat chronic wounds totalled $2.6bn in 2006. An annual growth rate of 12% is forecast over the next 5 years, bringing the market to $4.6bn in 2011.

Current Technology Landscape

Wound Healing

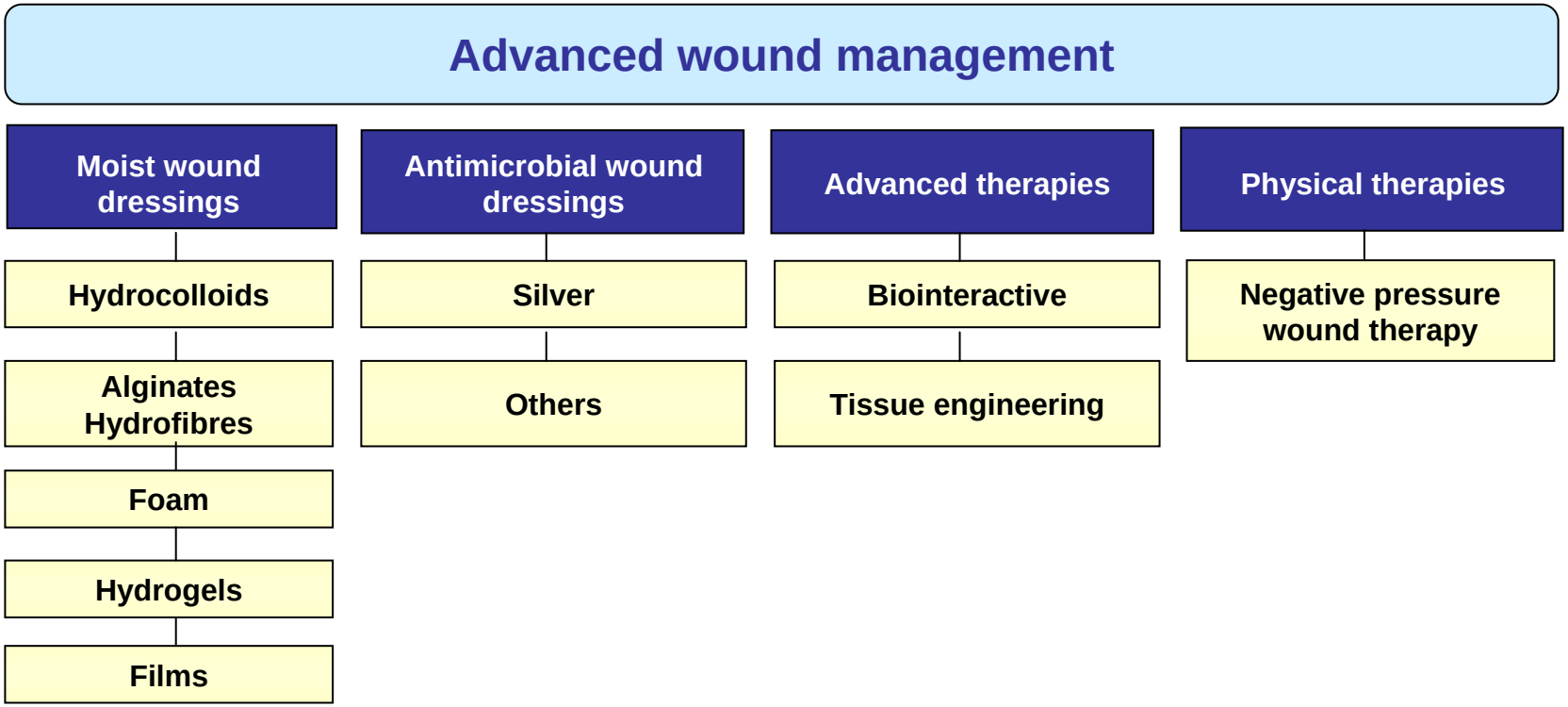
- Normal wound healing is a complex process that requires a series of interactions at the cellular and molecular levels to take place sequentially over a number of days to weeks and months.



- In chronic wounds, this process is disturbed and the wound becomes ‘stuck’ in the inflammatory phase for weeks, months or even years. The underlying cause of this problem has been, and continues to be, the subject of much research but it remains poorly understood, although infection at the wound site is known to keep the healing process in the inflammatory phase.
- Treatment of patients with chronic wounds encompasses a wide range of modalities from tools for diagnosis of the condition of the wound and its aetiology through to management of the symptoms and on to active interventions to assist the wound to heal.

Assisting the Wound to Heal

- A number of advanced wound management products currently on the market assist the wound to heal

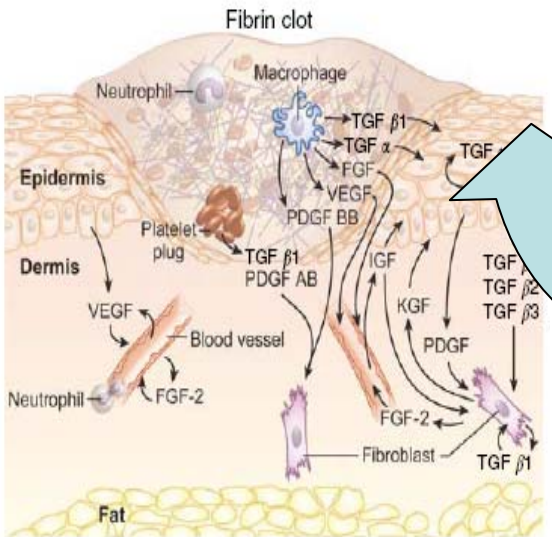


Technology Applications

- These technologies can be applied to help create the right wound bed environment, to stimulate the healing process or to manage symptoms.

Creating the right wound healing environment

- Debriding agents
- Moist dressings
- Antimicrobial dressings
- Physical therapies



Stimulating the wound healing process

- Advanced therapies
- Physical therapies

Symptom management

- Moist dressings
- Antimicrobial dressings
- Advanced therapies
- Pain-relieving agents

Technology Applications: TIMEX

- Smith & Nephew has developed the acronym TIME to describe the key elements involved in preparing the wound bed and encouraging the healing process. This provides a useful framework for understanding where wound care technologies are applied. It has been amended to reflect other aspects of wound healing, such as pain control with the addition of X (extra factors) to TIME.

Parameter	Proposed pathophysiology	Potential clinical solutions
T: Tissue non-viable or deficient Does the wound contain non-viable tissue, sometimes referred to as necrotic?	Defective matrix and cell debris impair healing	Debridement: enzymatic, autolytic Biological (larval therapy) Mechanical maintenance
I: Infection or inflammation Does the wound indicate signs of increasing bacterial contamination or inflammation?	High bacterial count or prolonged inflammation Inflammatory cytokine activity raised Protease activity raised Growth factor activity reduced	Debridement Antimicrobials (topical / systemic) Anti-inflammatories Protease inhibitors
M: Moisture imbalance Does the wound indicate the production of excess exudate or is the wound too dry?	Desiccation slows epithelial cell migration Excessive fluid causes maceration of wound margin	Moisture-balancing dressing Compression Topical negative pressure
E: Edge of wound non-advancing or undermined Are the edges of the wound undermined and is the epidermis failing to migrate across the granulation tissue?	Non-migrating keratinocytes Non-responsive wound cells and abnormalities in extracellular matrix Abnormal protease activity	Debridement Skin graft Tissue engineering Biological agents Physical therapies
X: Extra factors Is the patient experiencing pain?	Extrinsic pain caused by dressing change Intrinsic pain due to release of inflammatory mediators	Dressings with 'Low tack' adhesives Dressings with anti-inflammatories Systemic pain relief

Current Technologies: Moist Dressings

Moist Dressings

- Healing under moist conditions is significantly faster than under dry conditions. In fact, good hydration is believed to be the single most important external factor in achieving optimal wound healing. Traditional, non-occlusive dressings allow all moisture to escape from the surface of the wound. This eventually leads to wound drying, which slows re-epithelialisation and can lead to trauma due to dressing adherence. Surface drying also impedes the delivery of nutrition and immune defences to the wound surface and increases wound inflammation (exudate). The accumulation of exudate (excess liquid) at the wound surface is known to lead to maceration of both injured and healthy skin.
- The moist wound healing concept gave rise to the first advanced dressings. These dressings absorb excess exudate and allow evaporation of water vapour from the outside surface, thus allowing large quantities of exudate to be managed without maceration while maintaining the moist wound healing environment required for speedy healing. Semi-occlusive dressings also allow oxygen to reach the wound surface. The amount of exudate produced varies from wound to wound and a range of products has been developed that offer the practitioner a range of absorbencies.
- The moist wound dressing market is now nearing maturity and is already well served with the current marketed products. In 2007, the global market was estimated to be $1.44bn and predicted to reach $1.83bn by 2010 – a CAGR of 8%.
- Competition is intense, with major participants striving to maintain market share by offering discounts and bulk purchasing. To increase profits, manufacturers are creating hybrid products by combining two or more composites into one dressing or focusing on accurate exudate absorption.
- Moist dressings can be classified according to composition: films, foam, hydrogels, hydrocolloids and alginates.

Films

Market

Worldwide global market for films was estimated to be $230m in 2007

This market is fairly mature. The concept of using film dressings to control moisture is now over 20 years old and key patents are due to expire in the next few years

Technology

Films are composed of a polyurethane membrane coated with a layer of acrylic adhesive. They are semi-permeable and do not possess wound exudate absorption properties

Features: Suitable for superficial wounds, allow oxygen and moisture control

Benefit: Efficient as secondary dressing

Disadvantages: Difficult to place on wound, usage limited by low exudate absorption and lack of bacteriostatic properties

Applications: Pressure ulcers, minor burns, skin lacerations

Products

Key products include: Carrafilm (Carrington), Procyte (Bard), Epiview (Convatec), Transeal (De Royal), Bioclusive (J&J)

Hydrocolloids

Market

Worldwide global market for hydrocolloids was estimated to be $508m in 2007

This market grew rapidly in the 1980s and 1990s. There is now a trend towards conversion from hydrocolloid to foam dressings, which will erode the hydrocolloid market

Technology

Consist of absorbent materials such as pectin or xanthene gum, which are embedded in a matrix of adhesive material

Features: Can be categorised into: low exudate, medium exudate, high exudate, shaped hydrocolloids, composite specialist hydrocolloids and other specialist products

Benefits: Can absorb more fluid than films and so have extended wear time. Easy to apply.

Disadvantages: Odour, dressing can melt/disintegrate and adhere into the wound bed and lead to complications

Applications: Pressure ulcers, venous ulcers, necrotic wounds

Products

Key products include: DuoDerm (Convatec), Replicare (Smith & Nephew), Comfeel (Coloplast) and Tegasorb (3M)

Foams

Market

Worldwide global market for foam dressing was estimated to be $498m in 2007

Foam dressings have been long established in the market (first appearing in the late 1980s). The fastest growing segment in moist wound dressings – foams – is increasingly seen as the dressing of choice for dealing with exudate and is taking share from hydrocolloid dressings. This move towards foam is driven by the continuing development of the exudate management capacity of foam dressings, the line extensions for dealing with specific wound types, reduction in manufacturing costs (e.g. through relocation of manufacture to low-cost countries) and the conversion of less developed markets to moist wound healing

Technology

Foams are hydrophilic dressings generally made of polyurethane foam

Features: High exudate absorption, bacterial barrier due to polyurethane backing

Benefits: Can absorb greater amounts of exudate that hydrocolloids and so can remain in place for longer over moderate to highly exuding wounds. Do not break down or leave residue in wound bed. Moderate costs

Disadvantages: Application on low-exudate wounds could lead to drying

Applications: Moderate exudate wounds, pressure ulcers

Products

Key products include: Tielle (Johnson & Johnson), Allevyn (Smith & Nephew), Biatain (Coloplast)

Alginates

Market

Worldwide global market for alginate-based dressings was estimated to be $120m in 2007

Popular in the home care and extended care markets where high absorption capacity is used to reduce the number and expense of skilled visits

Technology

Alginates are derived from sea weed and are in the form of soft non-woven fibres. They can be moulded into pads, ropes or ribbon-like structures for wound healing

Features: High absorption capacity that is not significantly reduced by pressure or compression

Benefits: In deeper wounds, alginates conform to the wound bed and contain exudate better than foam dressings

Disadvantages: Could dry lightly exudating wounds and second dressing. Some products leave fibres in the wound that must be removed by irrigation. Require a secondary dressing to hold them over the wound bed

Applications: High exudate wounds, pressure ulcers, venous ulcers

Products

Key products include: Kaltostat (Convatec), Curasorb (Covidien), Comfeel-Sealsorb (Coloplast), Kalginate (De Royal)

Hydrogels

Market

Worldwide global market for hydrogels was estimated to be $71m in 2007

Technology

Hydrogels are a water-insoluble polymer chain network. They are super-absorbent natural or synthetic polymers, e.g. sodium polyacrylate, agarose and hyaluronan

Features: Provide moist wound surface due to high water content

Benefits: Provide a soothing cooling effect, which offers pain relief. Wound hydration

Disadvantages: Dressing absorbs less exudate and cannot be used for wounds with high exudate

Applications: Partial or thick wounds, necrotic wounds, burns, autolytic debridement

Products

Key products include: DuoDerm (Convatec), Aquasorb (De Royal), Purilon Gel (Coloplast)

Current Technologies: Antimicrobial Dressings

Antimicrobial Wound Dressings

- Treatment of wound infection is key in assisting the wound to heal. High levels of bacteria have been shown to inhibit every step in the wound healing process.
- Topical and systemic antibiotics have been used for many years to treat wound infections. However, there is a high level of concern about antibiotic resistance as wound bed conditions favour the development of resistant organisms. As a result of the growing resistance to antibiotics, antimicrobial dressings, which contain various antiseptic agents, are viewed as an alternative method for fighting antibiotic-sensitive and resistant wound pathogens.
- The global antimicrobial market was estimated to be worth $405m in 2007; this excludes antibiotics. The European market is worth almost double the US ($210 vs. $121m, respectively), which reflects the trend for clinicians in the EU to prescribe antimicrobial products compared to topical antibiotics in the US.
- The global market is predicted to experience considerable growth reaching $764m by 2010, a CAGR of 24%. This growth is driven by the emergence of 'super bugs' such as MSRA, the push for infection control and the increased awareness of infection.
- The antimicrobial market (excluding antibiotics) can be segmented into silver dressings and non-silver dressings.

Silver Dressings

Market

Silver dressings generated the highest revenue in the EU antimicrobial wound dressings market in 2007, with a 88% share in the overall revenues

Silver is increasingly being integrated with moist wound dressings to create hybrid dressings that provide healing advantages over single-agent dressings. Such hybrid dressings are experiencing the highest growth rates

Technology

Silver acts by disrupting DNA replication and cell division

Silver dressings are available in several forms, including silver-sulfadiazine-impregnated dressings and some that release ionic silver. The amount and rate of ionic silver released from different dressings varies. An initial release of high levels followed by sustained release appears to aid reduction in bacterial numbers

Features: Can be categorised according to release characteristics: high release (Acticoat), moderate (Silvercell), low (Aquacell) or non-release (Antisorb)

Benefits: Broad-spectrum activity, targets resistant bacteria, resistance to silver is rare

Disadvantages: Can lead to wound bed discoloration, systemic toxicity a potential concern

Applications: Antimicrobial action on low to high exudate wounds, ulcers, burns

Products

Key products include: Algidex Ag (De Royal), Aquacel Ag (Convatec), Acticoat (Smith & Nephew)

Non-silver Antimicrobial Dressings

Market

The non-silver segment accounted for 12% of the overall antimicrobial revenues in Europe (2007) and is experiencing over 20% growth annually

Although silver dressings are the most popular antimicrobial wound therapy, other therapies are expected to have good market potential and are witnessing investment from market participants. Some of these products are seen in an infection preventive role

Technology

Iodine-based dressings employ either povidone iodine or cadexomer iodine. Cadexomer iodine (a 3D starch lattice) is widely used because of the twin ability of the complex to kill microbes by cell wall and membrane disruption to deslough the debris through absorption

Polyhexamethylene biguanide (PHMB) is an antiseptic that is commonly integrated into gauze. It is also applied in combination with biosynthesised cellulose and acts mainly via pH imbalance, releasing lipopolysaccharides from the outer membrane

Chlorhexidine gluconate is a antiseptic that is impregnated in foam-based dressings. Its antimicrobial action is caused by membrane disruption of microbes

Other antiseptics, such as honey and acetic acid, are also being marketed

Features: Available in number of different forms (liquids, pastes, impregnated dressings etc). Method of use and frequency of application varies

Benefits: Relatively easy to use, widely available

Disadvantages: Impact on wound healing not fully understood

Products

Key products include: Huni (Comvita), Contreet (Coloplast)

Current Technologies: Advanced Therapies

Biointeractive Dressings

Market

The market for advanced therapies, which includes biointeractive dressings, was estimated to be $133m in 2007. However, estimates vary widely, with MedMarket estimating market-for-growth factors alone to be $206m in 2007

Technology

Polysaccharides: Polysaccharide dressings (e.g. maltodextrin, chitosan, β-glucan) can be applied as powder or paste and are thought to activate macrophages when placed in contact with the wounded area of the skin

Growth factors (e.g. PDGF) enable active cell proliferation and thus accelerate wound healing

Collagen and hyaluronic acid are important components of the extracellular matrix. They can polymerise *in vitro*, thereby enabling the development of several forms of dressing. Collagen has demonstrated protease binding activity

Features: Can take the form of a bandage consisting of bioactive materials to promote healing or alternatively material is designed to form a gel layer when in contact with the wound bed

Benefits: Stimulate wound healing

Disadvantages: Scope for unsolicited immune response, risk of cell number increase following growth factor treatment, requires supervision

Products

Key products include: Regranex (Ethicon), Autologel (Cytomedix), Multidex Gel (De Royal), GlucaTex (Genzyme), ColActive (Covalon), Urgocell (Urgo), Promogran (J&J)

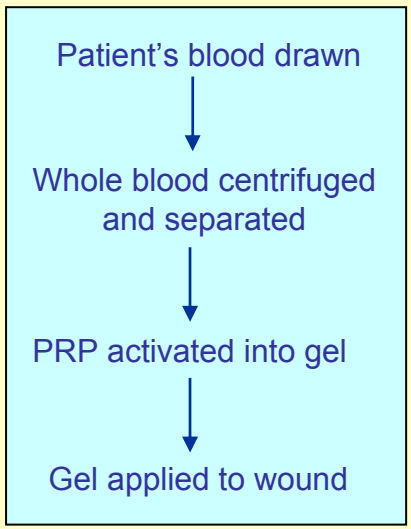
Biologics: Regranex

REGRANEX® GEL 0.01% (becaplermin)

- Regranex (becaplermin) is the lone growth factor wound healing product on the market in the US and Europe. It is a gel formulation of platelet-derived growth factor (rhPDGF-BB).
- Regranex is indicated for the treatment of lower-extremity diabetic neuropathic ulcers that extend into the subcutaneous tissue, or beyond, where there is an adequate blood supply. Regranex increases the incidence of complete healing of diabetic ulcers when used as an adjunct to good ulcer care practices, which include initial sharp debridement, pressure relief and infection control. It has not yet been established for the treatment of pressure ulcers and venous stasis ulcers.
- Regranex has equivalent biological activity to that of endogenous PDGF and acts by:
  - (i) stimulating angiogenesis and granulation tissue formation;
  - (ii) promoting the recruitment and proliferation of the chemotactic cells, including monocytes and fibroblasts, necessary for stimulation of a variety of wound healing processes and aiding in the creation of granulation tissue.
- However, concerns have recently been raised over product safety given the high doses employed. J&J have now issued a black box warning of an increased risk of cancer mortality in patients treated with three or more tubes of the product. Data from a retrospective study conducted using a health insurance database showed a five-fold increase risk of cancer mortality in these patients, although there was no overall increase in cancer incidence among the total number of 1,622 patients receiving Regranex vs. 2,809 controls.

Platelet-rich Plasma

- An alternative approach to single growth factor products such as Regranex is to use the body's own source of growth factors. Platelets are a rich source of growth factors, including PDGF, and are readily isolated from whole blood. Autologous platelet-rich plasma (PRP) is used in a variety of surgical and chronic wounds and is becoming relatively common-place in the US and Europe.
- The only autologous platelet gel therapy product with FDA clearance for broad indications is Cytomedix's AutoGel. However, the company has yet to secure CMS reimbursement in the US and has agreed to a post-market surveillance study to monitor the safety of the bovine thrombin used in the system.

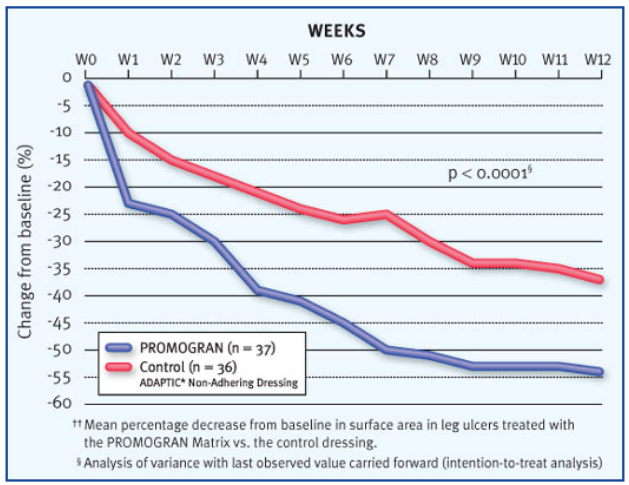


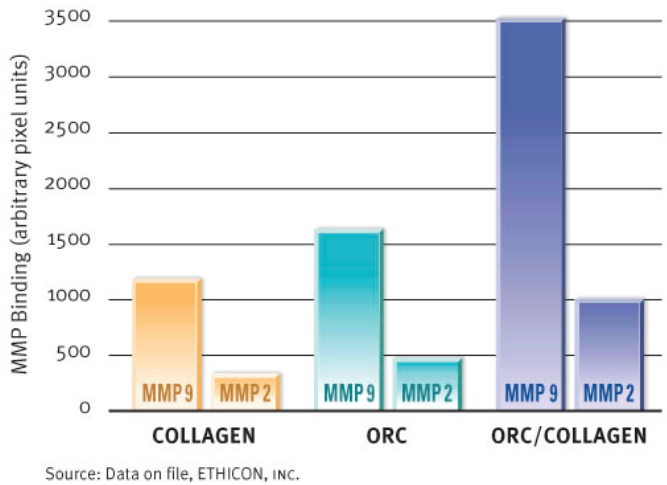
Cytomedix™ AutoloGel™ SYSTEM

- The AutoloGel™ System is intended to be used at point-of-care for the safe and rapid preparation of platelet-rich plasma (PRP) gel from a small sample of a patient's own blood.
- Under the supervision of a healthcare professional, the PRP gel produced by the AutoloGel™ System is suitable for exuding wounds, such as leg ulcers, pressure ulcers and diabetic ulcers, and for the management of mechanically or surgically debrided wounds.

Proteases: Promogran

- Research interest around matrix metalloproteinases (MMPs) is increasing following the recent advances in our understanding of the role of MMPs in delayed wound healing. MMPs play a key role in normal wound healing, including the removal of damaged extracellular matrix components, angiogenesis, migration of epithelial cells, contraction of wound matrix and remodelling of scar tissue.
- However, researchers have now shown that chronic wounds are characterised by elevated levels of inflammatory cells that secrete MMPs and other proteases, which degrade proteins essential for healing.
- Therapies that reduce protease synthesis or reduce or inhibit activity have been developed. Diagnostics, which rapidly indicate protease activity of wound fluid, are now in development.
- Promogran Matrix is marketed by Johnson & Johnson. The product combines oxidised regenerated cellulose (ORC) and collagen, which has been proven to bind MMPs in the dressing more effectively than ORC or collagen alone. It is claimed to create a wound-bed environment conducive to granulation tissue formation, epithelialisation and rapid wound healing.





Current Technologies: Tissue Engineering

Tissue Engineering

- Skin grafts have been used for a number of years for the treatment of burns. The process accelerates wound healing; the underlying dermis is nourished with capillaries, which carry a rich bank of cells that – post grafting – tend to multiply and replace the wounded tissue.
- Skin grafts can be divided into three main categories:
  - autografts – where the patient's own skin is harvested from a donor side;
  - allografts – where skin is harvested from cadaver donors, typically by non-profit organisations;
  - xenografts – where skin from other animal species is used.
- However, tissue harvest and transplantation have a number of disadvantages, such as the risk and expense of surgery, donor site morbidity, the risk of disease transmission and potential rejection. As a result, tissue engineering techniques have been developed to create skin replacements or substitutes as alternatives to conventional grafting technologies.
- Skin tissue engineering technology was initially developed for the treatment of extensive burns. The success of these skin replacement products for this indication led many to focus on their potential application for the treatment of chronic wounds.
- However, the high cost and perceived marginal benefits over advanced wound dressings have proved to be significant barriers in the application of skin tissue engineering technology in non-life-threatening situations such as chronic wounds. As a result, many big players have avoided this space. Indeed, Smith & Nephew sold two of its products (Dermagraft and TransCyte) to Advanced BioHealing. Dermagraft was once viewed as Smith & Nephew's most exciting new product. However, poor sales – despite its clear efficacy in the treatment of diabetic foot ulcers – led the company to divest the product in 2005.

Tissue Engineering

Market

The market for advanced therapies, which includes tissue engineering, was estimated to be $133m in 2007. However, estimates vary widely with MedMarket reporting the global skin tissue engineering market to be worth $115m in 2007, predicting it to reach $359m by 2016

The market is limited by the high cost of these products. They are significantly more expensive than other advanced therapies and require strong cost-effectiveness claims to ensure adoption

Technology

There are three main types of biological skin replacement:

(i) epidermal (keratinocytes grown in tissue culture or on a carrier)

(ii) dermal (fibroblasts or endothelial cells grown on a support structure)

(iii) composites (integrated cultures including mixed cell types)

Associate technologies, such as support carriers/matrices and tissue scaffolds, are necessary

Features: Skin substitutes can be temporary or integrated (partially or fully). Material source can vary and can be autologous, allogeneic or xenogeneic. Various organisations provide skin substitutes, including: hospital in-house labs, not-for-profit organisations (e.g. tissue banks), service providers (grow-up and return samples of the patient's tissue) and product providers.

Benefit: Acceleration of healing of full-thickness wounds

Disadvantages: High cost, handling and storage difficulties, risk of infection, cannot be used on infected wounds

Applications: Full-thickness wounds, burns and diabetic ulcers

Key Products

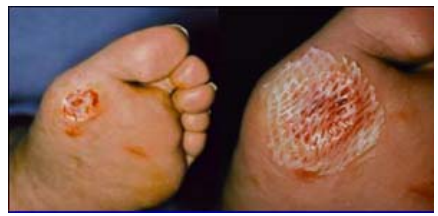
Product (company)	FDA-Approved Indications (PMA, HDE, 510K or other)	Competitive advantages	Disadvantages
Alloderm (Lifecell)	Burns/full-thickness wounds (allograft)	Not rejected; no cases of viral transmission after >100,000 product applications; 2 year shelf life	Lacks cellular components
Celaderm (Advanced Biohealing)	None	>6 month shelf life; relatively inexpensive; good results in many pilot studies	Not yet FDA approved
Dermagraft (Advanced Biohealing)	Diabetic foot ulcers (PMA); ulcers secondary to epidermolysis bullosa (HDE)	Mimics function of dermis; cryopreserved product	Difficult logistics of ordering and application; short shelf life unless cryopreserved
Epicel (Genzyme)	Deep partial-thickness and full-thickness burns (HDE); congenital nevi (HDE)	Autologous cells; no rejection; high incidence of permanent take	Fragile; custom preparation; 1 day shelf life; inferior cosmesis in many patients
EZ Derm (Eurosurgical)	Porcine xenograft (510K). Partial-thickness burns; venous, diabetic and pressure ulcers	Relatively long shelf life	Potential immune response and / or disease transmission
Integra (Integra Life Sciences)	Deep partial-thickness and full-thickness burns (PMA)	Two layers; good barrier function; used in over 10,000 patients; moderate shelf life	Operative removal of silicone layer and autograft required
OrCel (Forticell)	Split-thickness donor site (PMA); mitten hand deformity surgery of epidermolysis bullosa (HDE)	Mimics cytokine expression of healing skin; 9 month shelf life cryopreserved	Requires cryopreserved storage
TransCyte (Advanced Biohealing)	Full- and partial-thickness burns (PMA)	1.5 year shelf life frozen	Silicone membrane must be removed

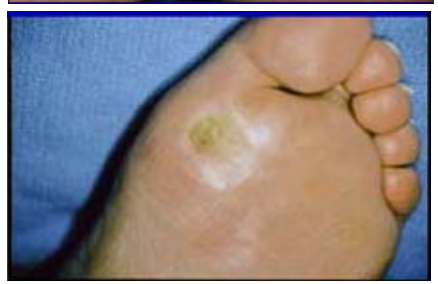
Apligraf

- Apligraf is the tissue engineering market leader developed and manufactured by Organogenesis.
- Apligraf is a bi-layered skin substitute consisting of living cells and structural proteins. The lower dermal layer combines bovine type I collagen and human fibroblasts (dermal cells), which produce additional matrix proteins. The upper epidermal layer is formed by promoting human keratinocytes (epidermal cells) first to multiply and then to differentiate to replicate the architecture of the human epidermis. The keratinocytes and fibroblasts are claimed to produce over 40 cytokines and growth factors that are involved in the development, regeneration and healing of skin and are thought to play a central role in the effectiveness of the technology in healing chronic wounds. The manufacturing process takes 20 days.
- Apligraf is indicated for the treatment of venous leg ulcers along with standard compression therapy and full-thickness diabetic foot ulcers. Organogenesis claims Apligraf heals 30–50% more foot or leg sores in a third less time than conventional wound care (compression therapy).
- Organogenesis filed for bankruptcy in 2002. While revenue was increasing, the cost of producing Apligraf exceeded sales due to the high costs associated with low unit volume production. The company underwent a period of reorganisation and emerged from chapter 11 protection towards the end of 2003.

Organogenesis inc.
LIVING TECHNOLOGY

Treatment Sequence





Current Technologies: Physical Therapies

Physical Therapies

- This segment is dominated by mechanically assisted wound closure devices, particularly the Vacuum Assisted Closure (VAC) device from Kinetic Concepts, Inc. (KCI).
- Sales of VAC have grown extraordinarily, coming from nowhere in 1995 to being a billion-dollar product and leading the advanced wound management market in 2006. VAC accounts for the majority of all the sales in this category.
- Sales of VAC will continue to increase through continued development of the market, particularly outside the US, and the introduction of line extensions focusing on portability and patient convenience. KCI has also recently licensed rights to a topical anti-infective solution technology from NovaBay Pharmaceuticals, which it plans to combine with the VAC system.
- A recent entrant into this market is Smith & Nephew, which purchased Blue Sky Medical in 2007 and is now marketing the V1STA Negative Pressure Wound Therapy System. The negative pressure technology has been and continues to be the subject of patent litigation between KCI and Blue Sky Medical. This appears to be resolving in a way that allows KCI and Smith & Nephew to continue marketing their products but makes it very difficult for new entrants in this segment.

Negative Pressure Wound Therapy

Market

The market for negative pressure wound therapy was estimated to be worth $1.9bn in 2007. Double-digit growth is predicted with the market expected to reach $3.24bn in 2010

Technology

The use of sub-atmospheric pressure to promote or assist wound healing and to remove fluids from a wound site. The process involves the use of a vacuum pump and creates a hypoxic environment for bacteria, thereby eliminating aerobic microbial activity. The removal of bacteria increases the oxygen content required for tissues to heal the wound. The therapy removes the slough and necrotic tissue and promotes wound closure in 5–10 weeks. It is also reported to improve blood flow to the wound

Features: Vacuum-based therapy, drains fluid from wound, creates sterile environment for wound healing

Benefits: Potential to accelerate healing process via number of mechanisms of action

Disadvantages: Likely to impede the patient's mobility

Applications: Diabetic ulcers, pressure ulcers, complex chest wounds, hospital-treated wounds, open abdominal wounds. Its potential application as adjunct to skin grafting and skin substitute application is also being explored

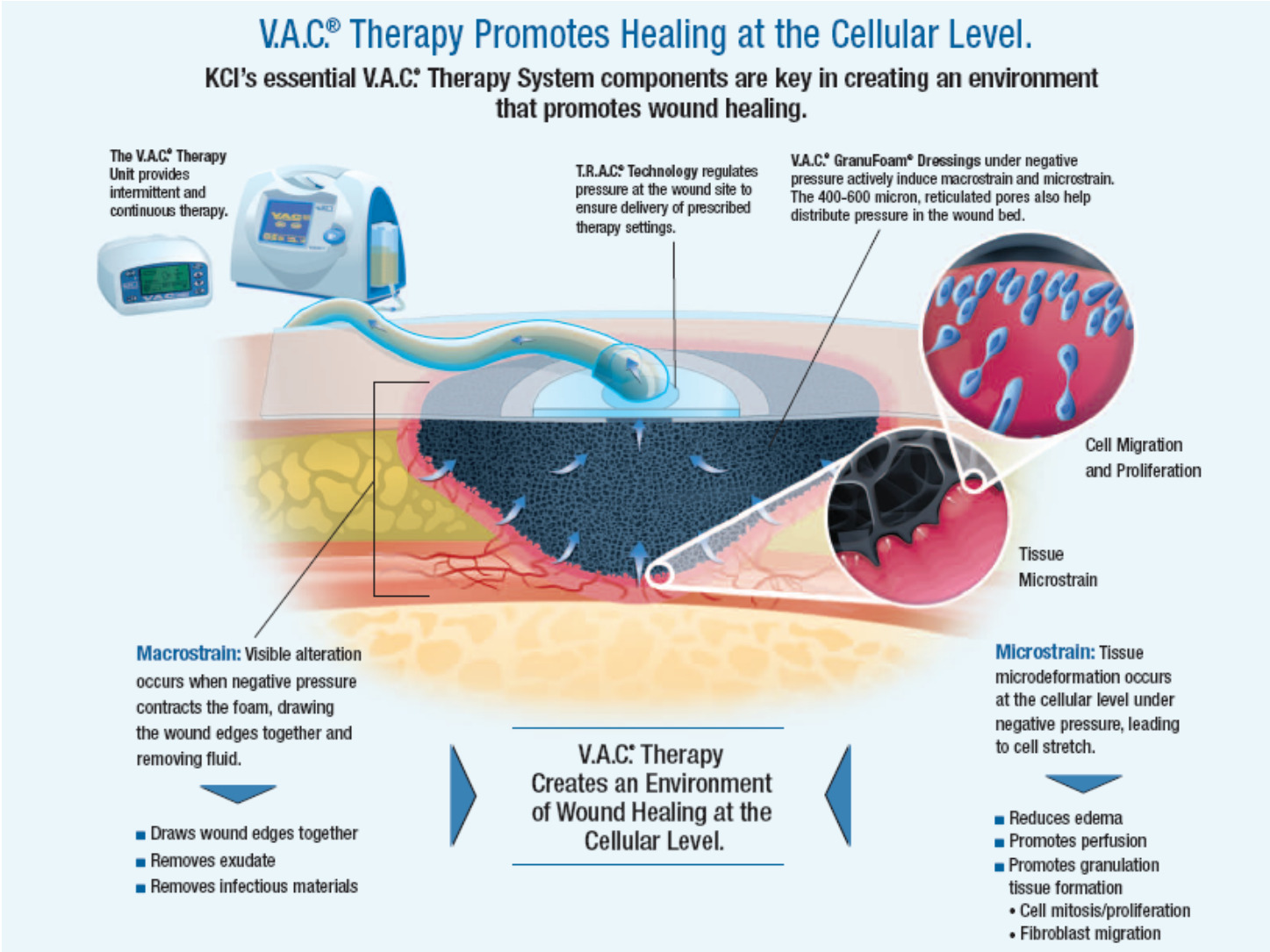
Products

Key products are VAC Therapy (KCI) and Vista Versatile 1 (Blue Sky / Smith & Nephew)

KCI's VAC Technology

- The VAC device allows the controlled application of sub-atmospheric pressure to a wound using a therapy unit to intermittently or continuously convey negative pressure to a specialised wound dressing to help promote wound healing.
- The device consists of a computer-controlled therapy unit, canister, sterile plastic tubing, foam dressing and adhesive drape. The foam dressing is placed on or inside the wound and the tube attached and sealed with the adhesive drape. The tube is connected to the VAC system and vacuum applied.
- The hydrophobic, open pore structure of GranuFoam Dressings (400–600 micron pore size) adapts to the contours of deep or irregularly shaped wounds in order to provide equal distribution of pressure at the wound site and allow optimal circulation of fluids around wound edge.
- KCI recommends that VAC system remains on for at least 22 out of 24 hours per day. Patient mobility is limited, even though the new ActiVac system is light weight and designed to provide a higher level of mobility, being 34% lighter, 36% smaller and with a 17% longer battery life (14 hours).
- KCI has established two methods for connecting multiple wounds to one therapy unit: 'Bridging' and 'Y-connecting'. Bridging can be accomplished when you have multiple wounds of similar pathology in close proximity to one another. The tubing is placed in a central location and one pump used to distribute pressure throughout all the wounds. Y-connecting allows treatment of multiple, non-infected wounds, that are a larger distance apart by using a connector that can support two separate tubing connections. Therapy in either situation is evenly distributed across the wounds, yet controlled by one pump.

Mechanism of Action



VAC Cost Savings

- Apelqvist *et al.* recently completed a randomised, controlled trial comparing the direct economic costs of care for patients treated with VAC and with standard moist wound therapy (MWT).
- The study cohort (*n* = 162) comprised diabetic patients with post-amputation wounds.
- The authors concluded that treatment of NPWT resulted in lower resource utilisation and a greater proportion of patients obtaining wound healing at a lower overall cost of care that MWT.

Factor	VAC	MWT
Surgical procedures	43	120
Dressing changes	41	118
Out-patient visits	4	11
Healed	43	33
Average direct cost to achieve healing	**$27,270**	**$36,096**
Average total cost to achieve healing	**$25,954**	**$38,806**

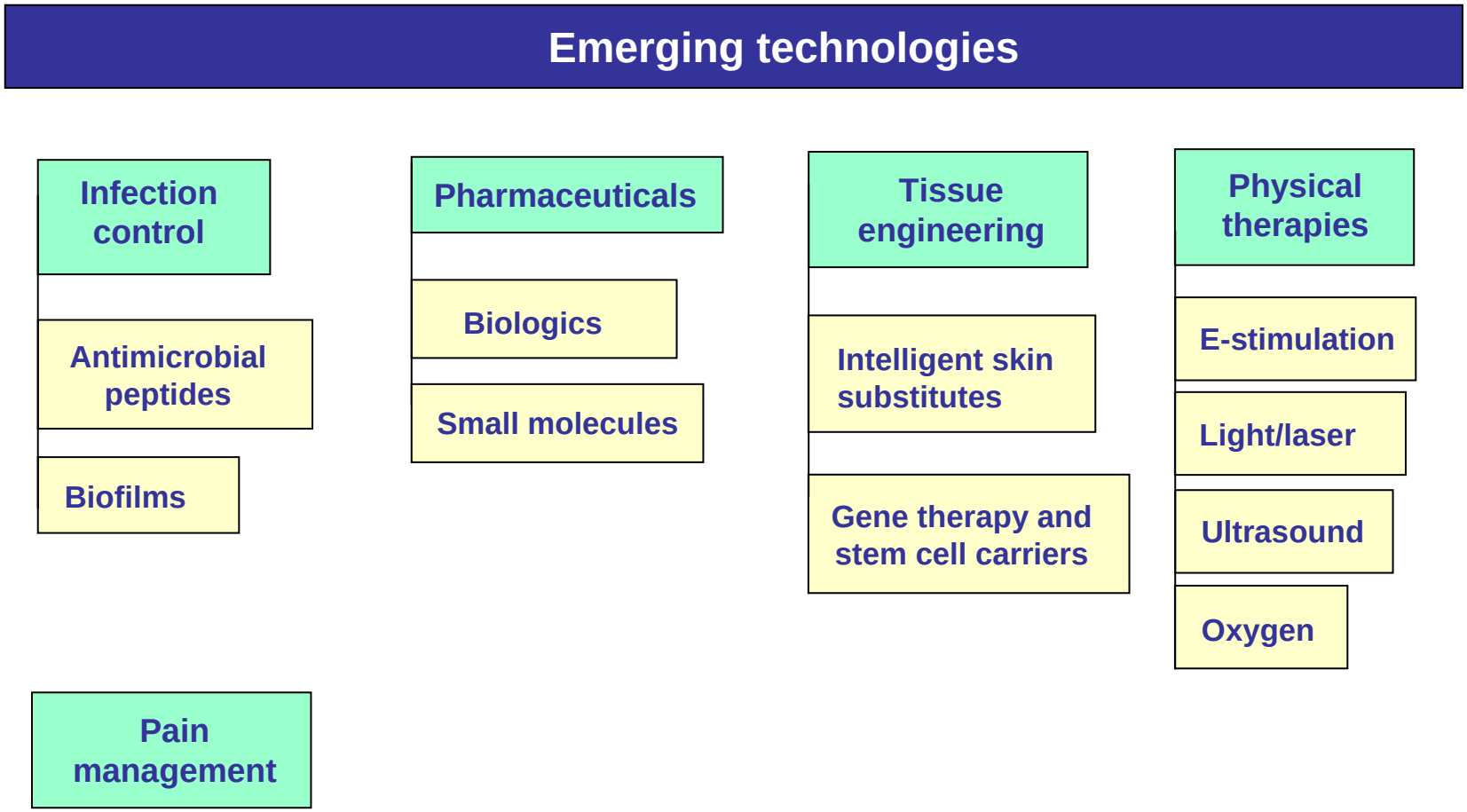
Other studies	Savings cited
Pressure ulcers Philbeck TE. Ostomy wound management 1999; 45 (11): 41–50	**$8,919**
Chronic wounds The Weinberg Group. Report prepared for Latham & Watkins, May 1999	**$1,925**
Orthopedic, abdominal, infected wounds Gould LJ. 2nd World Union of Wound Healing Societies Meeting, 2002	**$7,435**

S&N VISTA Technology

- Smith & Nephew's negative pressure wound therapy technology is KCI's main competitor in negative pressure therapy.
- The V1STA device consists of a therapy machine, canister, tubing, gauze dressing and clear film dressing.
- The gauze dressing is applied to the wound bed and attached to the therapy machine using the tubing and canister. The film dressing is applied to the top of the dressed wound and the therapy machine draws excess fluid from the wound into the canister.
- The device should remain on at all times and contains a back-up battery to enable the user to disconnect from mains for short period. As a result, patient mobility can be significantly restricted.
- Therapy duration varies from patient to patient depending on the size and type of wound but can take several weeks.
- Dressings need to be changed 2–3 times a week.
- The technology was developed by Blue Sky Medical, which was acquired by Smith & Nephew in 2007.

Emerging Technologies

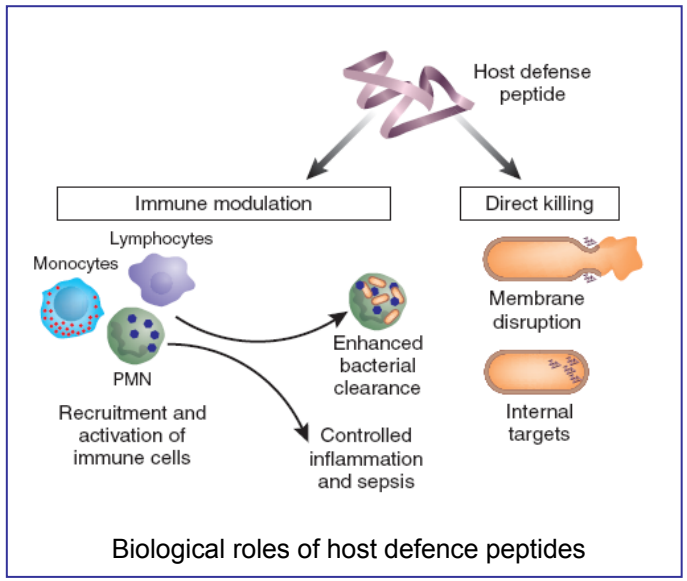
Emerging Technologies



Emerging Technologies:
Novel Antimicrobials & Biofilms

Novel Antimicrobials

- There is increasing concern about the development of bacterial resistance to antibiotics. Antiseptics are also used to treat infection and whereas resistance to antiseptics, such as silver, is unlikely they are non-specific in action and so might have toxic effects on human cells involved in the healing process. As a result, there is a need for a new class of antimicrobials.
- Antimicrobial peptides (AMPs) have been proposed as a potential new generation of antibiotics. They are generally defined as peptides with less than 100 amino acid residues and an overall positive charge (+2 to +9) imparted by the presence of multiple lysine and arginine residues and by a substantial portion (>30%) of hydrophobic residues.
- More than 800 AMPs have been isolated from a wide range of organisms. In addition, thousands of synthetic variants have also been produced.
- These can be classified according to structure:
  - α-helical;
  - β-sheet;
  - loop;
  - extended peptides.
- AMPs can also be classified according to mechanism of action:
  - membrane disruptive;
  - non-membrane disruptive (intracellular targets).
- These peptides are also innate immune modulators and so are often referred to as 'host-defence peptides' to illustrate both their broader functions in innate immunity and their antimicrobial activity.

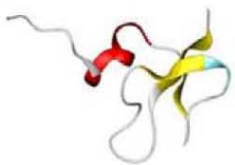


Biological roles of host defence peptides

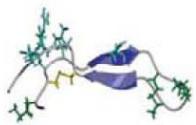
Selected Structures

- Examples of some well-studied AMPs originating from a range of sources and representative of the main structural classes:

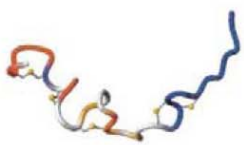
Magainin 2
class:alpha-helical
species: Xenopus laevis
activity:Gram+ & Gram-, Fungi, Cancer cells



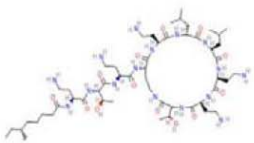
beta-defensin 3
class:all beta
species: Homo sapiens
activity: Gram + & Gram -



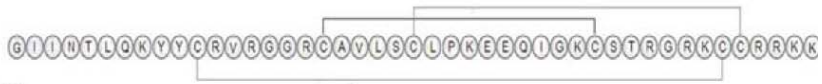
Lactoferricin B
class:beta-hairpin peptide
species: Bos taurus
activity:Gram+ & Gram-, Fungi, Virus, Cancer cells

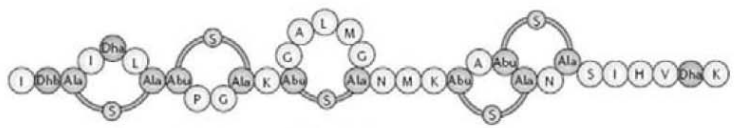


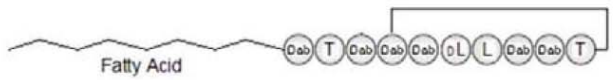
Nisin A
class:non regular peptides
species: Lactococcus lactis
activity:Gram+



Polymyxin E (Colistin)
class: cyclic polypeptides
species: Bacillus colistinus
activity:Gram-







Advantages

Broad-spectrum activity

- AMPs have antimicrobial activity against a wide range of micro-organisms:
  - *Bacteria*: antimicrobial activity against both Gram +ve and Gram –ve bacteria and multi-drug-resistant bacteria.
  - *Viruses*: reportedly inhibit the replication of enveloped viruses such as influenza A and HIV-1.
  - *Tumour cells*: some AMPs have been reported to be cytotoxic to MDR cancer cells and to have minimal side-effects compared to other chemotherapeutic agents. These have been shown to rapidly kill cancer cells, be unaffected by classical chemotherapy resistance mutations, show synergy with conventional chemotherapy, destroy primary tumours and prevent metastases, to be independent of cell proliferation and can be used to destroy non-dividing tumour cells.
  - *Protozoa, yeast and fungi.*

Immunomodulatory activity

- As well as antimicrobial activity, AMPs also possess immunomodulatory activity including modulation of expression of 100s of genes in monocytes, epithelial cells and others, direct chemoattraction of immune cells, induction of chemokines and differentiation responses, promotion of angiogenesis, wound healing responses and resolution of infections.
- Innate immunity is an ideal antimicrobial therapy as it is rapidly acting, relatively non-specific and involves a package of effector mechanisms making resistance development unlikely. However, overstimulation would lead to sepsis.

Potential adjunct therapy

- AMPs might also enhance potency to existing antibiotics *in vivo* by facilitating access of antibiotics into the bacterial cell. They are also thought to neutralise endotoxins.

Advantages … continued

Low likelihood of resistance

- Many believe that acquisition of resistance of a microbial strain to AMPs is highly improbable, as AMPs have remained effective against bacterial infections for over 10^8 years.
- However, certain microbial pathogens will be inherently more resistant to AMPs than others, as a result of stable structural or functional properties or pathogenesis strategies. For example, resistant species of genera such as *Serratia* express an outer membrane that lacks the appropriate density of acidic lipids required to provide peptide-binding sites. Other organisms, such as *Porphyromonas gingivalis*, secrete digestive proteases that destroy peptides.
- Furthermore, many believe that peptides will eventually induce resistance. Perron *et al*. recently demonstrated that resistance can evolve rapidly whenever bacterial populations are consistently exposed to elevated levels of AMPs. This is of concern, as it may lead to cross-resistance to innate human antimicrobial peptides. However, several observations mitigate these concerns: (i) all knock-out animals are reportedly healthy with only modest alteration in susceptibility to infection; and (ii) cross-resistance of mutants to other peptides appears to be limited.

Wide number of potential applications

- In addition to treating wound infection, AMPs have a wide number of additional applications, given their broad antimicrobial spectrum of activity. For example, researchers have proposed their use as catheter coatings, imaging probes for bacterial infections, ‘chemical condoms’, aerosol delivery to treat lung infections. However, toxicity concerns might restrict systemic applications and limit the technology to topical delivery.

Technology Challenges

Challenge	Critical need	Strategies
Pharmacology	Improve half-life *in vivo.* Peptides are susceptible to proteolytic degradation	Peptidomimetics Modified and/or D-amino acids, amidation at the *N*-terminus Non-natural amino acids New formulations (e.g. liposomal) Immune-modulating peptides may not require regular dosing
Toxicity	Toxicity concerns likely to limit applications to topical treatments in first instance. Need to understand mechanisms of toxicity	Assess subtle toxicities such as apoptosis induction and mast-cell degranulation Toxicogenomics Toxicology in animal models
Screening	Larger variety of peptides with improved stability and toxicity as well as bactericidal activity	Peptide arrays for increased diversity. Recent technology advances now permits the production and screening of up to 50,000 peptides per pipetting robot per year New natural lead molecules Peptide-like (mimetic) approaches Non-natural amino acids Screen for both antimicrobial and immune-modulating activities
Cost of goods	Lower the cost. Cost price of synthetic peptides is 5–20x that of conventional antibiotics	Make shorter analogues that work Recombinant manufacturing processes Natural sources (e.g. lantibiotics) Immune-modulating peptides might require smaller doses
Efficacy	Improve activities in context of model infections	Realistic animal models of disease In-vitro assays at physiological conditions In-vitro models to predict immune modulation

New Candidates in the Pipeline

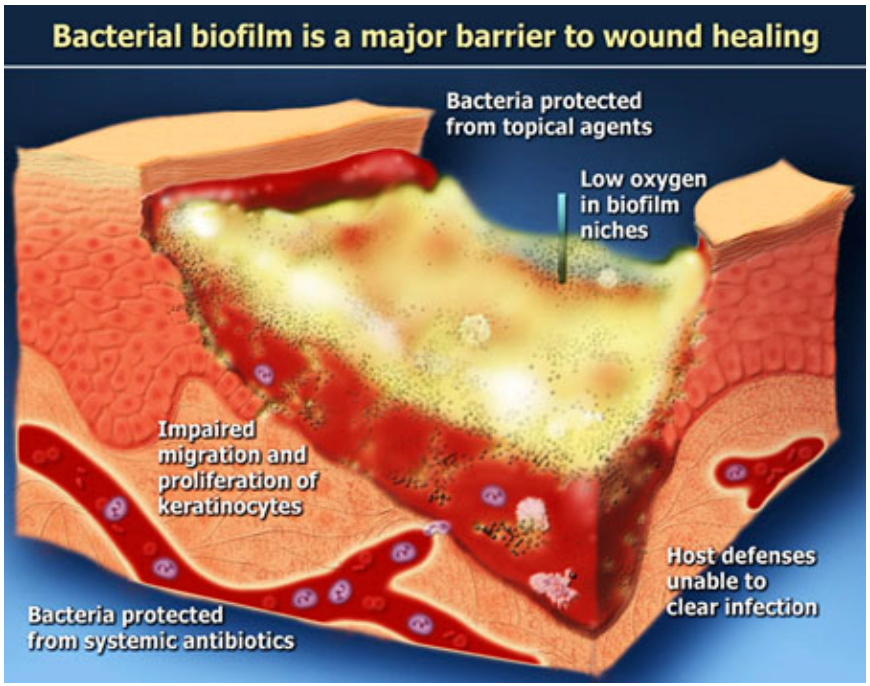
- The cationic peptides polymyxin B and gramicidin S have been used in the clinic and as topical OTC medicines for some time. Furthermore, cationic lantibiotic nisin is used as an antimicrobial food additive.
- A number of peptides and peptidomimetics are in commercial development, examples of which are listed below.

Company	Candidate	Application	Comments
BioLineRx (Jerusalem)	BL2060	Anti-infective	Synthetic compound comprising fatty acid and lysine copolymers. Lead optimisation
Helix Biomedix (Washington)	HB-107	Wound healing	19-amino-acid fragment of cecropin B Preclinical
Polymedix (Philadelphia)	Peptidomimetics	Anti-infectives; antimicrobial polymers and coatings	Derived from arylamide, calixarene, hydrazide and salicylamide series Discovery/preclinical
Novabiotics (Aberdeen, Scotland)	NP213	Antifungal	Lead antifungal preclinical Antimicrobial peptides in discovery
Novacta Biosystems (Hatfield, England)	Mersacidin	Gram-positive infections	Preclinical

- Pexiganan, a 22-amino-acid analogue of magainin 2, was the first antimicrobial peptide to undergo development as topical treatment of diabetic foot ulcers. Macrochem acquired exclusive worldwide license rights to Genaera's Pexiganan in October 2007. Genaera had conducted two Phase III trials. However, outstanding issues with chemistry, manufacturing and controls, and an FDA request for an additional controlled trial, prevented approval.

Biofilms

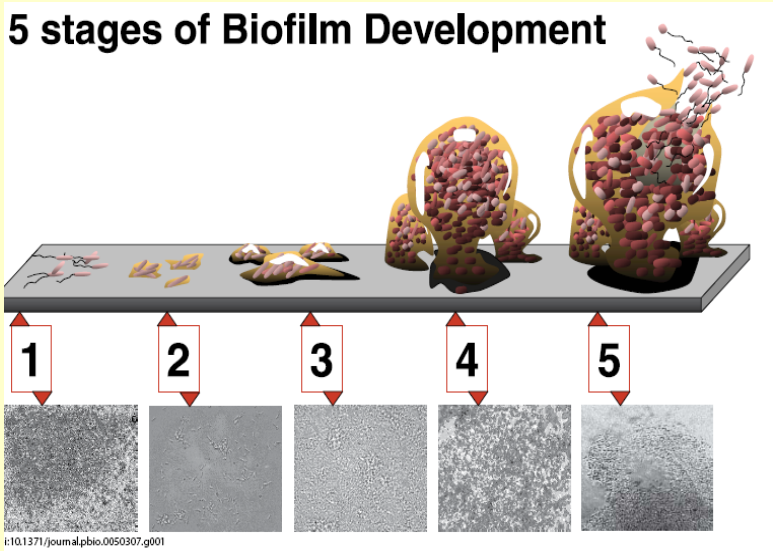
- A biofilm is a population of bacteria that is attached irreversibly to various biotic and abiotic surfaces and encased in a hydrated matrix of exopolymeric substances, proteins, polysaccharides and nucleic acids.
- Bacteria in a biofilm behave differently from their free-floating (planktonic) counterparts. They surround themselves with a complex polymeric matrix, often simply termed 'slime'. As it grows thicker, the film often includes many bacterial species and the matrix develops a complex structure.



- This slimy matrix protects the bacteria from assaults from immune cells. Thus they become resistant to phagocytosis, which makes them difficult to eradicate. In addition, they are often highly resistant to UV irradiation and desiccation.
- The bacteria are highly resistant to conventional antibiotic therapies and an antibiotic concentration 100 to 1,000 times normal can be necessary to control an infection, despite the fact that some antibiotics can readily diffuse through the slimy matrix. The reason for this resistance is not fully understood, although the bacteria in biofilms rarely divide and so antibiotics such as penicillin, which need to be incorporated into the cell wall, will be ineffective.

Biofilm Formation & Persistence

- Biofilm formation is a complex developmental process involving attachment and immobilisation on a surface, cell-to-cell interaction, microcolony formation, formation of a confluent biofilm and development of a 3D biofilm structure.



Stage 1: initial attachment. Stage 2: irreversible attachment. Stage 3: maturation I. Stage 4: maturation II. Stage 5: dispersion. Each stage of development is paired with a photomicrograph of a developing *P. aeruginosa* biofilm.

- The biofilm starts when a few pioneer cells use specialised chemical hooks to adhere to the surface and help make the target surface more attractive to subsequent cells.
- A number of environmental factors, such as glucose, iron and pH, influence biofilm formation.
- The bacteria have a cell-to-cell communication mechanism that co-ordinates gene expression when the population has reached a high cell density; this is termed quorum sensing.
- Once the biofilm is established, it develops a complex structure in which different cells occupy distinct environments where, for example, levels of acidity, oxygen and iron can vary. Therefore, the bacteria experience different environmental conditions and as a result have different physiologies. This physiological and genetic diversity means that a single antibiotic approach is unlikely to be successful.
- Small groups of 'persister' cells, which survive immune or antibiotic attack, are common. These survivors feed off the dead bacteria and rapidly re-establish the film once the assault is over.
- The final stage of the biofilm lifecycle is autodispersal, when regions of film spontaneously disperse as cells dissolve the matrix by secreting enzymes and revert to their planktonic form.

Innovation Potential

- A few researchers are now proposing biofilms to play a pivotal role in the development of chronic wounds due to the heightened inflammatory response observed as the host tries (unsuccessfully) to eliminate the biofilm. These researchers have gone so far as to propose biofilm formation to be the best unifying explanation for the failure of chronic wounds to heal.
- However, many wound care specialists remain sceptical even about biofilm existence. Recent studies have employed scanning and electron microscopy techniques to demonstrate biofilm presence in the wound bed. Indeed, a recent study reported biofilms to be present in 60% of those chronic wounds examined. These findings may alleviate some of this scepticism.

Need for new biofilm detection methods

- Currently, there is no routine way of detecting biofilms. They are not visible to the naked eye and culture techniques cannot confirm whether any bacteria grown have formed a biofilm. Scanning and electron microscopy are excellent research tools but are not suitable for use in the clinical setting. As a result, there is a need for new methods to detect the presence of a biofilm.

Need for improved therapeutic strategies

- In addition to new diagnostic techniques, there is also a need for improved therapeutic strategies. Debridement is now believed to aid wound healing, at least in part, through the removal of these biofilms. However, there is still innovation potential around the development of new strategies to tackle biofilms.
- Several therapeutic strategies have been proposed. These are discussed on the following slide.

Innovation Potential

- **Development of agents to disrupt the formation or survival of the film:** These could be used in conjunction with existing antibiotics, antiseptics or novel antimicrobial agents and would perhaps be more suited to cutaneous wounds than internal infections.

- **Exploiting biofilm-related pathways:** Quorum sensing has been proposed to be a critical pathway for forming biofilms. Targeting these bacterial signalling pathways might therefore be one strategy for tackling and disrupting biofilms. However, recent studies have shown that mutant bacteria, which are unable to perform quorum sensing, are still able to form a biofilm. The role of quorum sensing in biofilm formation needs to be better understood.

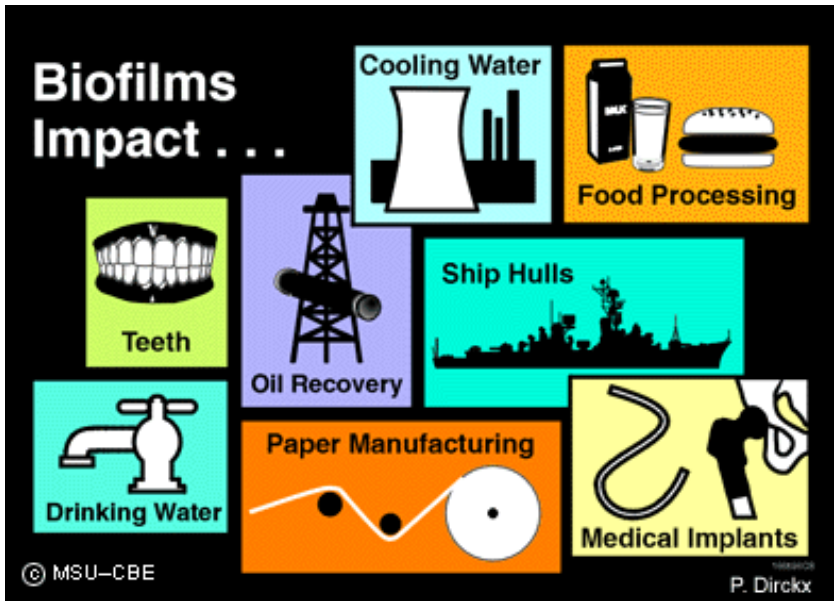
- **Developing an autodispersal inducer:** Researchers have identified a signalling molecule that triggers autodispersal, which appears to be universal across bacterial species. However, applications may be limited as instantaneously releasing billions of bacteria in their planktonic form may not be advantageous for widespread infections, although it could be more safely employed in localised infections.

- **Bioelectric effect:** Weak electric fields are believed to enhance the efficacy of antibiotics against bacterial biofilms.

- **Utilising bacteriophages:** Researchers at Boston University have genetically engineered natural viruses by adding genes for enzymes that attack the slime. The phages first hijack the bacterial machinery to replicate themselves, then break the cells open to release the copies, and also the enzyme. These engineered phages were shown to be 100 times more effective that the phages alone.

Not Just Wounds

- Biofilms are not just a wound-related phenomenon but are a key feature of other conditions, such as cystic fibrosis, and are also known to negatively affect implant functioning.
- In addition to the healthcare sector, biofilms also impact industries such as petroleum, specialty chemicals, household products, drinking water, mining and utilities. Indeed, microbial biofilms on surfaces are believed to cost the US billions of dollars a year in equipment damage, product contamination, energy losses and medical infections.
- Conversely, microbial processes at surfaces also offer opportunities for positive industrial and environmental effects, such as bioremediating hazardous waste sites, biofiltering industrial water and forming biobarriers to protect soil and groundwater from contamination.



Emerging Technologies: Biologics & Small Molecules

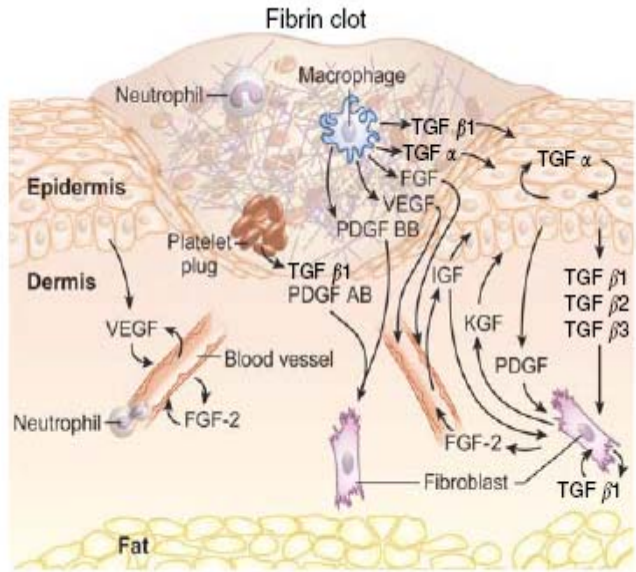
Biologics

- Regranex becaplermin is the lone growth factor wound healing product on the market in the US and Europe. Regranex is a gel formulation of platelet-derived growth factor (rhPDGF-BB). It promotes the chemotactic recruitment and proliferation of cells involved in wound repair and enhances the formation of granulation tissue.
- The wound healing potential of several other growth factors has been studied, including epidermal growth factor (EGF), fibroblast growth factor (FGF) and transforming growth factor (TGFβ). These factors play roles in cell division, differentiation, proliferation and organisation. It is interesting to note that many of these proteins are targets of potential anticancer agents seeking to stop the spread of tumour cells.
- This sector is littered with failures, with many candidates failing during development, e.g. Genzyme's TFGβ2. The most recent casualty is Genentech's Telbermin – a recombinant vascular endothelial growth factor (VEGF) for the topical treatment of diabetic foot ulcers. Genentech ceased development of the topical treatment in 2007 following poor Phase II trials results.
- There are many theories for the lack of clinical success. The heterogeneity, and therefore variability, in chronic wounds coupled with improvements often noted in the control group make clinical efficacy difficult to demonstrate. Understanding why the failure rate is so high may serve to highlight technology challenges and therefore innovation potential.

Why Do They Fail?

Complexity and multifactorial nature of chronic wounds

- A chronic wound is a complex problem involving sequential interaction between numerous proteins, cells and signals. There is a deficiency of not just one but several growth factors, as well decreased collagen synthesis, poor vascularisation and increased matrix metalloproteinases. As a result, the application of a lone biologic is unlikely to be highly effective.
- Agennix is taking a novel approach and developing a single factor (talactoferrin alpha) that is thought to release a number of key cytokines and to stimulate multiple growth factors. In this way, a single applied factor might influence a number of factors and wound healing pathways.
- There is also a lack of understanding of the wound healing process and the interactions, timings and requirements for various growth factors. This could provide an opportunity for developing sensing technologies to identify the deficiency and the optimal treatment regime.



Initiation of wound repair

Why Do They Fail?

Delivery and stability of biologic agents

- Proteases, matrix metalloproteinases and inflammatory cells rapidly digest and denature peptides and so stability is an issue. Researchers have shown that less than 10% of an applied growth factor (FGF and EGF) reaches a depth of 1–3 mm. As a result, greater doses of agent must be applied (with significant cost implications). Poor stability also leads to poor compliance due to the extensive re-applications required. Regranex is applied to the wound and allowed to sit for 12 hours before being washed off and re-applied.
- Large proteins struggle to penetrate the necrotic, poorly vascularised wound bed and hit healthy tissue. This is particularly problematic when developing agents targeting angiogenesis.
- There may be an opportunity to develop improved delivery technologies. Tissue Therapies, for example, has developed a platform technology to deliver growth-enhancing factors to cells, tissue and patients via a complex based on the protein vitronectin. The company views wound healing as a lead application. Its VitroGro technology contains domains of vitronectin linked to IGF-1. Being synthetic significantly reduces manufacturing costs. The VitroGro technology can be sterilised through irradiation at 50 kGy and has a 2-year shelf-life when stored at 20^{o}C. It has been shown to hold the growth factor close to the cell surface, thus protecting the biologic from protease degradation.
- Safety concerns given the supra-physiological doses currently used to combat delivery issues may prove to be a future barrier to use and increase the need for improved delivery technologies. In June 2008, J&J issued a black box warning of an increased risk of cancer mortality in patients treated with three or more tubes of Regranex. Tissue Therapies' technology addresses this concern, currently employing around one-tenth of the growth factor (in this case IGF) used in previous trials, while obtaining a similar effect.

New Agents in Pipeline

- Despite the low success rate, some companies remain convinced that single growth factors have a role to play as evidenced by new candidates currently in development.

Company	Products	Technology	Comments
CardioVascular BioTherapeutics (Las Vegas)	CVBT-141B	Topical formulation of FGF-1 in a honey-like solution	Phase I diabetic foot ulcers (DFU) and venous leg ulcers (VLU)
Cardium Therapeutics (San Diego)	Excellarate	Topical gel using gene-activated matrix technology for sustained release of PDGF	Phase II for DFUs in collaboration with Tissue Repair Company
Celltran (Sheffield, England)	Lyphoderm	Lysate of freeze-dried human cultured keratinocytes containing a mix of natural growth factors	Acquired technology following mergering with XCELLentis. Inconclusive clinical reported in 2005. This company went into administration May 2008
Renovo (Manchester, England)	Prevascar (interleukin 10), Juvista (TGFβ3), Zesteem (17β estradiol)	Recombinant proteins for antiscarring and wound healing applications	Entering Phase III or in Phase II
Agennix (Houston)	Talactoferrin alpha	Recombinant protein formulated into topical gel	Successful Phase II in DFUs
Advanced Medical Solutions (Cheshire, England)	In development	Modulators of matrix metalloprotease activity	J&J lead this field with their Promogran MMP binding dressings
University of Pennsylvania	PDGF	Injectable PDGF gene therapy	Phase I DFU
RegeneRx (Bethesda)	Thymosin beta 4	NF-kappa B	Phase II. Pressure ulcers, corneal wounds

Small Molecule Candidates

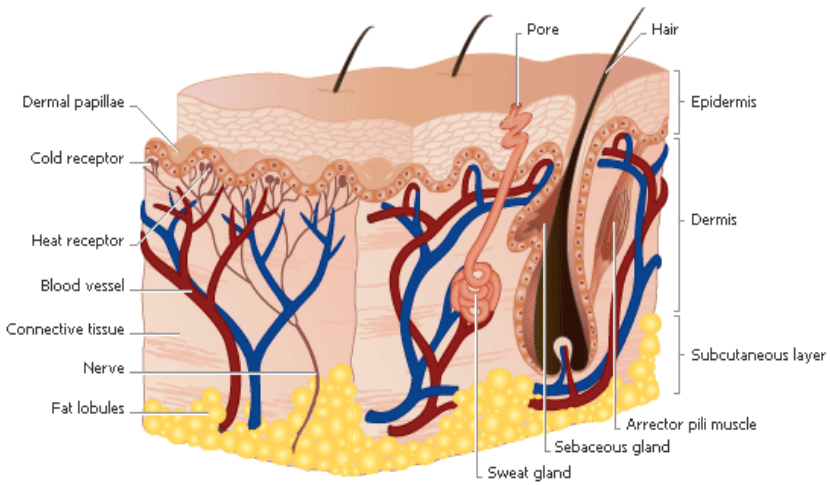
- A number of companies are investigating the potential of small molecules, which can act as ligands to signal the desired effect.
- These have the advantage of improved delivery and stability compared to biologics. However, like biologics, they have an increased regulatory burden compared to other technologies and the financial consequences would be considerable if the single target approach lacked the required efficacy in wound healing indications.
- One route to market for a wound healing pharmaceutical product is through assessing wound healing abilities of drugs presently marketed for other indications. This is the case with Actelion's Tracleer (Bosentan), which is an oral dual endothelin receptor antagonist. This has previously been approved and marketed for treatment of pulmonary arterial hypertension but has now been approved in the EU for the treatment of digital ulcers in scleroderma patients.

Company	Product	Technology	Comments
Actelion (Switzerland)	Tracleer	Oral dual endothelin receptor antagonist	Approved in EU for narrow indication
CytRx Corp (San Diego)	Iroxanadine	Oral small molecule that amplifies molecular chaperone proteins to enhance the cell's ability to repair proteins	Planned Phase II 2008
King Pharmaceuticals (Bristol, TN)	MRE0094	Topical selective agonist for adenosine A2A	Phase II for DFUs. Acquired from Medco Research in 2000

Emerging Technologies: Tissue Engineering

Technology Requirements

- The ultimate goal of tissue engineering is rapidly to produce a construct that offers the complete regeneration of functional skin, including all the skin appendages (hair follicles, sweat glands and sensory organs) and layers (epidermis, dermis and fatty subcutis) with rapid take (vascularisation) and the establishment of functional vascular and nerve networks and a scar-free integration into the surrounding host tissue.
- Such a construct should allow the skin to fulfil its many functions: barrier formation, pigmentary defence against UV irradiation, thermoregulation, mechanical and aesthetic functions. Some, but not all, of these functions are restored with existing skin substitutes.
- In addition, skin substitutes should have some essential characteristics such as:
  - easy to handle and apply
  - provide vital barrier function with appropriate water flux
  - readily adherent
  - appropriate physical and mechanical properties
  - undergo controlled degradation
  - sterile, non-toxic, non-antigenic, non-inflammatory
  - facilitate angiogenesis
  - minimise scarring and pain
  - cost effective



Current Technology Limitations

- Although increased healing rates of burn and / or chronic wounds can be observed with current engineered constructs, several intrinsic shortcomings limit their use. Key limitations are listed below:

1. Epidermal grafts are fragile and therefore difficult to handle; they require skilled application
2. Cell-populated matrices used in skin substitutes are not readily scaleable for manufacturing; quality control is challenging
3. Transport and storage can be an issue as many are cryopreserved
4. Can be susceptible to contractures
5. Stability, rate of degradation and persistence of cells
6. Failure to vascularise
7. Scarring at graft margins
8. Absence of differentiated structures
9. Autografts require creation of fresh wounds
10. Allografts and xenografts can carry infectious agents, including prions
11. They typically promote healing of chronic leg ulcers by only around 25% over patients receiving standard care
12. High cost and perceived marginal benefit

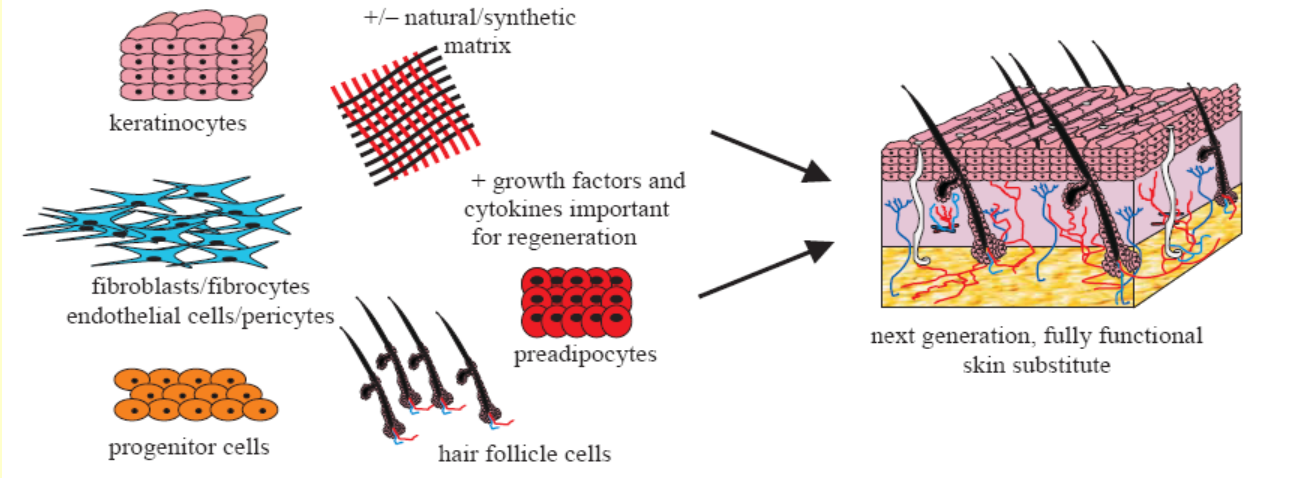
- These limitations suggest that further improvements are needed to ensure that tissue-engineered constructs are more effective, lower cost, user friendly and carry minimal risk of infection.

Construct Building Blocks

The basic building blocks of the construct are:

1. **Biopolymer:** This must be biocompatible and biodegradable.
2. **Biomimetics:** These are selected to add function to the biopolymer. The bioactive function may be cell-binding activity, growth factor activity, growth-factor-binding activity, enzymatic activity or enzyme-binding activity.
3. **Cells (optional):** Cells added exogenously to the engineered biopolymer may be used to induce a functioning tissue substitute. When an acellular biopolymer is implanted, it must contain sufficient information within the engineered construct to support endogenous tissue cell in-growth and appropriate differentiation for tissue formation.

Schematic of the requirements to create a fully functional skin substitute



Innovative Approaches

Two main approaches are currently being considered for development of the next generation skin substitutes:

1. **Highly engineered approach:**

   - One approach to delivery of next-generation substitutes is development of an intelligent skin substitute. This would take the form of a biomaterial scaffold engineered to release various signalling molecules, differentiation factors and protein domains in a time-dependent fashion to facilitate cell migration and adhesion. These substitutes could be further engineered to produce various 3D patterns and densities.

2. **Minimally engineered approach:**

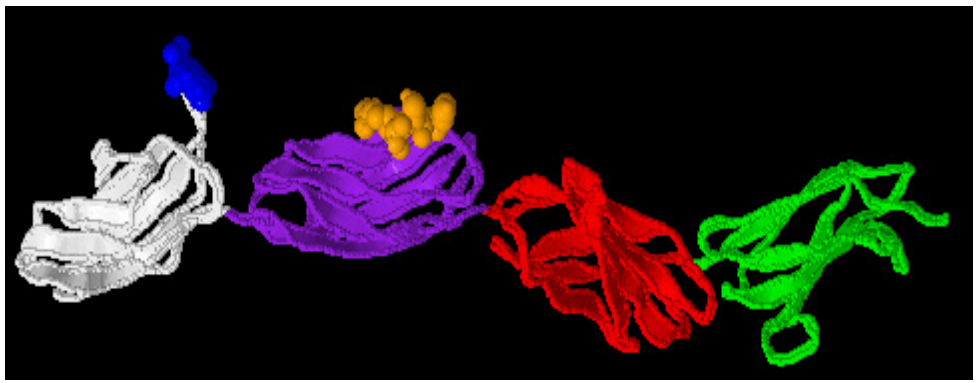
   - In this instance, the requirement would be for a minimally engineered construct that fulfilled the role of an easy-to-handle carrier. This carrier could be seeded with stem cells, which would function as the agents of tissue repair, or alternatively act as a scaffold for gene transfer or as a source of genetically altered cells.

- In addition, researchers are examining the advantages and disadvantages of synthetic vs. natural polymer backbones. The biopolymer is required to provide mechanical support for cell migration and proliferation. These scaffolds can be fabricated from either naturally derived or synthetic materials with corresponding advantages and disadvantages.

Natural vs. Synthetic Scaffolds

Naturally derived materials

- Naturally derived materials have several advantages over synthetics. They provide biological stimuli to support cell and tissue function (e.g. collagen, fibrin), have mechanical properties similar to natural tissues and are biodegradable (e.g. gelatine).
- However, they have several disadvantages, such as increased risk of viral infection, antigenicity, unstable material supply and limited versatility in manipulating properties.
- The most frequently used natural scaffolds for tissue engineering are fibronectin and collagen, although hyaluronan is gaining increased attention. Hyaluronan has proven biological activity but, unlike other natural materials, can be chemically modified to create a variety of stable derivatives and can also be produced by bacterial synthesis thus avoiding need for animal extraction.



Fibronectin type III repeats

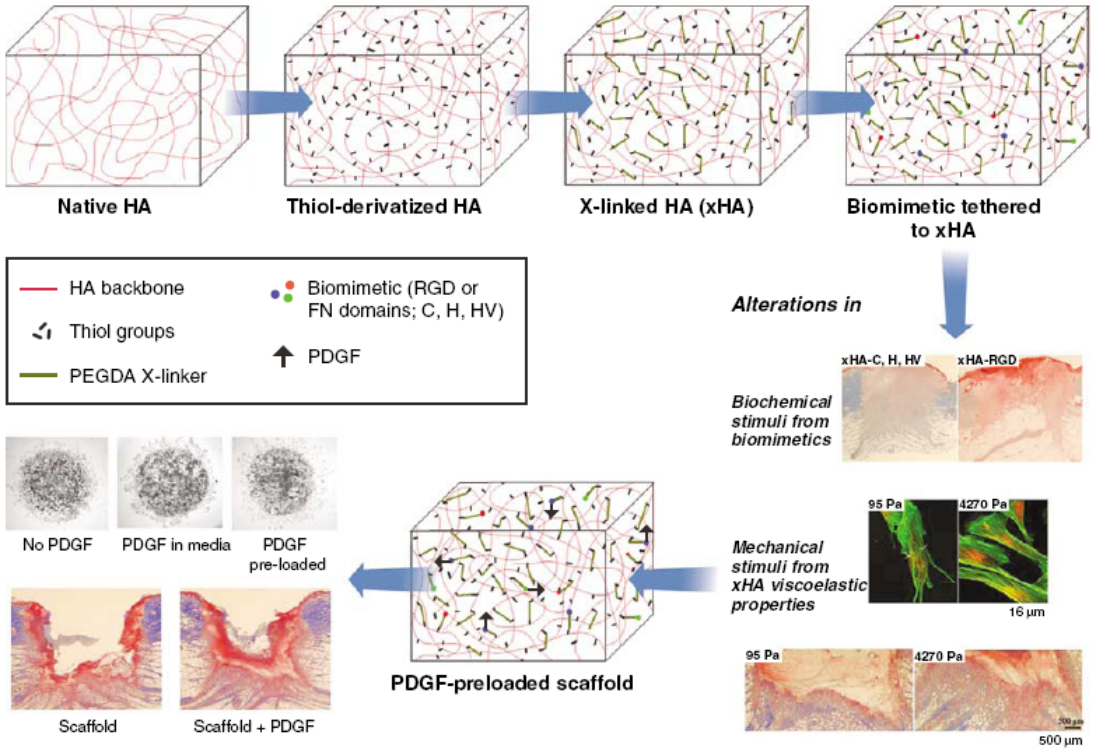
Natural vs. Synthetic Scaffolds

Synthetic materials

- Synthetic materials should provide mechanical support sufficient to withstand in-vivo forces and maintain potential space for tissue development until the regenerated tissue has enough mechanical integrity to support itself.
- They have several advantages over naturally derived materials, in particular their ability to be manufactured reproducibly on a large scale. They can also be processed into exogenous extracellular matrix (ECM) where the macrostructure, mechanical properties and degradation time can be readily controlled and manipulated. Fabrication from biodegradable polymers is also possible, although the first generation of biodegradable polymers was adapted from other surgical uses and has deficiencies in terms of mechanical and degradation properties. New classes of biodegradable materials are currently being developed.
- Their greatest disadvantage is the lack of cell-recognition signals. Several researchers are addressing this through incorporation of cell-adhesion peptides (and other molecular signals) into biomaterials. This is important, as mechanical signals conveyed to cells via their adhesion to the matrix also regulate the development of tissues and gene expression. An additional challenge is how to fabricate the polymers into scaffolds that have defined shapes and optimal porous architecture to direct tissue growth. New technologies are emerging that enable manufacture of materials of defined pore size, e.g. 3D printing and electrospinning.
- The concept of combining synthetic materials with molecular signals able to guide the cellular response is attractive. Such synthetic materials with biological functionality could also remove the requirement for cell seeding and lead to the development of an efficacious acellular construct or ‘intelligent scaffold’.

Acellular Construct

An acellular, functionalised, tissue-engineered biopolymer for the acceleration of cutaneous wound healing



Homobifunctional polyethylene glycol (PEG) derivates were added to thiol-derivatised hyaluronan (HA-DTPH) to intermolecularly cross-link hyaluronan (xHA) and also tether fibronectin functional domains (FN) to the xHA. *Biochemical stimuli from biomimetics*: xHA tethered with FN accelerated healing whereas xHA tethered with RGD (a stable peptide sequence from fibronectin) inhibited healing. *Mechanical stimuli from xHA viscoelastic properties*: less stiff xHA (95 Pa) failed to support full spreading of cultured fibroblasts whereas stiffer xHA (4270 Pa) provided support. The PDGF-preloaded scaffold further increased the rate of healing.

Minimally Engineered Construct

- Research is also focused on development of a minimally engineered construct that fulfils the role of an easy-to-handle carrier for stem cells or gene therapy agents.

Stem cells

- The carrier should hold the cells in an undifferentiated state prior to delivery and then degrade in the body by non-inflammatory dissociation. The degradation process should allow the cells to interact in similar fashion as during embryonic development or adult regeneration.
- Skin is an ideal model system for the investigation of the use of stem cells as a source of cell-replacement therapy because it contains one of the few well-characterised adult stem cell types – keratinocyte stem cells. One of the key technology challenges here lies in the isolation and characterisation of these cells. Another source of multipotent skin stem cells is the hair follicle bulge. Bone-marrow-derived mesenchymal stem cells have also been used as a source for cells to seed skin substitutes to accelerate wound healing.
- Falanga *et al.* recently showed topical delivery of autologous bone-marrow-derived cultured mesenchymal stem cells in a fibrin spray to accelerate healing of both murine and human cutaneous wounds.
- Further research is required to develop strategies to control stem cell differentiation in a robust and reproducible manner before viable products can be developed.

Minimally Engineered Construct

Gene transfer

- Engineered scaffolds have been proposed to provide a platform for healing using the scaffold to hold gene transfer agents.
- For example, Swiss researchers have recently begun to explore the potential of hypoxia-inducible factor-1α (HIF-1α) gene therapy in stimulating wound healing. HIF-1α induces expression of VEGF, which induces angiogenesis. Peptide-DNA nanoparticles containing HIF-1α δODD (oxygen-sensitive degradation domain) were entrapped in fibrin matrices and applied to full-thickness dermal wounds in the mouse. Significant angiogenesis was noted, with the maturity of the vessels induced by HIF-1α significantly higher than that induced by VEGF protein.
- Cardium Therapeutics is developing Excellerate, a DNA-based topical collagen gel formulated with an adenoviral vector encoding PDGF BB. In Phase I/II studies, more than 80% of patients with diabetes who received a single dose or four once-weekly doses had complete wound closure after 14 weeks. The technology was acquired from Tissue Repair Co. in 2006 and is now moving into Phase IIb trials for diabetic foot ulcers.

Emerging Technologies: Physical Therapies

Physical Therapies

- KCI has created a new paradigm in wound care where devices are now an accepted modality in addition to dressings and biologics. However, KCI's dominant patent position in NPWT highlights the need for alternative device technologies, as few will be able to follow Smith & Nephew into the negative pressure market.
- There is the potential for other technologies to deliver new physical therapies and the race is on to develop the next VAC. These include electrical stimulation, electromagnetic stimulation, ultraviolet therapy, oxygen therapy, ultrasound and laser-based devices.
- Many of the technologies on which these systems are based have been around for many years and so perhaps should not be termed 'emerging'. However, there is still potential for innovation here as there has been a tendency to by-pass the fundamentals and jump straight to development of suboptimal products. As a result, the scope for innovation lies in the optimisation of such devices. This will require an improved understanding of the mechanism of action.
- The mode of action and effectiveness of many of these technologies remain under debate. The absence of convincing evidence of the effectiveness of these physical therapies is at least partly responsible for their lack of commercial success to date.
- However, it is worth noting that VAC did succeed, despite the initial absence of data from controlled clinical trials. The rapid adoption of this technology by physicians can be attributed to the clear and tangible positive effect on wound progress that it generates.

Physical Therapies

- Industry scepticism of the alternative physical therapies is undoubtedly the biggest challenge facing this segment. This has largely arisen due to the development of a generation of suboptimal products with little or no supporting clinical data and so questionable efficacy. Randomised, controlled trials will be required to overcome the industry and physician scepticism.
- This segment has also struggled due to the lack of device homogeneity. A diverse range of stimuli, dosing strengths and treatment regimes are used, which makes it difficult to compare similar products.
- Although there is innovation potential through the optimisation of treatment regime, this is a relatively mature area. As a result, it is a crowded and competitive space with a complex patent landscape. It will be important to ascertain freedom to operate and ability to gain a secure patent position before entering this market.
- The next slides discuss leading alternative physical therapy areas: electrical stimulation, light/laser, oxygen and ultrasound.

Electrical Stimulation

- Direct current (DC) electric fields are present in all developing and regenerating animal tissues.
- Human skin maintains a transepithelial potential (TEP) across the epithelial layers. When the skin is cut, a large steady electric field (EF) arises immediately at the wound edge as current pours out of the lesion from underneath the wounded epithelium. This wound-induced EF persists until the migrating epithelium reseals the wound and re-establishes a uniformly high electrical resistance, at which point the wound-induced EF drops to zero.
- These fields measure around 140 mV/mm and are believed to play a role in controlling aspects of the cell biology of wound healing.
- Enhancing the endogenous wound-induced electric field has been shown to alter the frequency of cell division. Electric field strength also determines the direction and type of cell migration. Indeed, researchers have shown the polarity of EF to determine whether a wound closes or opens up. Authors concluded that physiological EF is at the head of a hierarchy of cues that interact to promote wound healing and that an electric field can over-ride and dominate the healing influences of normal sources of chemical gradients and of a free wound edge.
- Applied EFs with a wide variety of stimulation protocols have been used clinically to treat non-healing skin wounds. Many studies have claimed success but industry remains sceptical as many of these experiments were of poor design.
- Furthermore, it appears that clinical practice has proceeded before the cell biology of EF-directed wound healing was fully understood. As a result, suboptimal devices were brought to market with limited efficacy again giving rise to industry scepticism.
- Many believe that the optimal stimulation protocol to treat skin wounds with an applied DC EF is yet to be determined and will only be achieved once our understanding of cell biology improves.

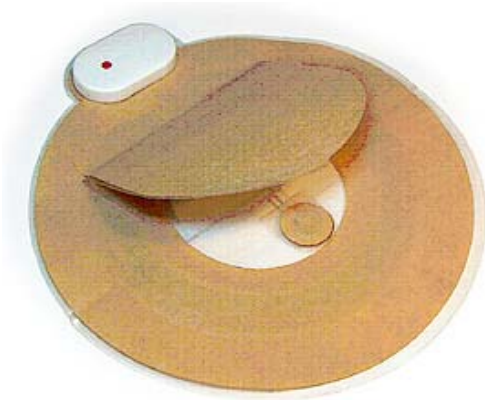
E-stimulation: POSiFECT

POSiFECT® biocurrent therapy (Biofisica LLC)

- The POSiFECT® innovation lies in the unique, patent protected bioelectric monitor that generates electrical current that mimics the body's naturally occurring electrical currents to stimulate the wound healing process.

How does biocurrent differ from traditional 'E-STIM'?

- Biocurrent therapy delivers constant exogenous current (CEC), measured in microamps, which is 1000 times lower than traditional electrical stimulation therapy.
- Most traditional electrical stimulation therapy devices deliver AC/DC currents measured in milliamps, three orders of magnitude higher than biocurrent.
- The electrical field is derived from two 3-V nominal lithium coin cell batteries, which enable it to deliver a constant direct microcurrent (DC) to the wound bed.
- POSiFECT® is supported by clinical case studies but as yet (and in common with many other products in wound care) lacks the support of controlled clinical trials.



Financing

- Biofisica closed on $5 million in Series A Financing in October 2006. The funds were to be used to help launch POSiFECT® in the UK. The company obtained a commitment of $2.3m in financing from investors in April 2008, which will support Biofisica's continued marketing efforts in the UK and ongoing planning initiatives in the US. The round was led by Unilever Technology Ventures, Novartis Venture Funds, the ATDC Seed Capital Fund.

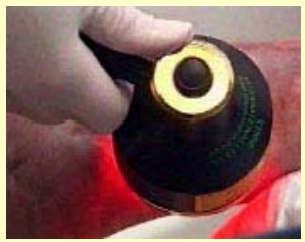
Light Emission Therapy

- Light therapy involves the application of red light and near infrared (IR) radiation to stimulate healing and relieve pain. The most commonly used terms to describe the therapy include: low-level laser therapy (LLLT), low-intensity laser therapy (LILT), low-energy photon therapy (LEPT) and phototherapy. A more recently accepted term for the effects of light therapy is photobiomodulation.
- The mechanism of photobiomodulation by red to near-IR light at the cellular level has been ascribed to the activation of mitochondrial respiratory chain components, resulting in initiation of a signalling cascade that promotes cellular proliferation and cytoprotection.
- Preclinical studies show a number of effects, including changes in cell proliferation, collagen biosynthesis and gene expression. The therapy is also thought to increase formation of new capillaries, improve lymphatic activity and offer pain relief. However, this technology cannot be applied to patients with photosensitive skin or porphyria.
- Convincing efficacy data generated from properly controlled clinical studies in wound healing are scarce. Technology needs to be supported with large-scale scientific data before it will gain acceptance from the wound care community.

Biolight

The Biolight device from Biolight International AB delivers pulsating monochromatic light and is marketed for a number of indications, including chronic wounds. The device had promising results in the Phase II clinical studies but these did not reach statistical significance.

THOR
THE FUTURE OF MEDICINE



Thor has developed a low-level laser therapy device that applies red and near-IR light over injuries or lesions to improve wound/soft-tissue healing and give relief for both acute and chronic pain.

Oxygen Therapy

- Hyperbaric oxygen therapy is considered to have some success in healing difficult wounds and is used to a limited extent to stimulate wound healing. However, it requires high-capital-cost equipment and is inconvenient for the patient. Recently, there has been the development of portable (non-hyperbaric) products that concentrate oxygen from the atmosphere, such as Epiflo (Ogenix) and O_2 Boot (GWR Medical, Inc.). These offer localised treatment thus bypassing the potentially harmful effects of hyperoxia.

- Oxygen is believed to play a key role in:
  - metabolic support – to sustain cellular processes;
  - matrix repair – supporting tissue regeneration;
  - antisepsis/infection control – inhibition of anaerobic bacteria;
  - signalling and control of cell responses – activating repair mechanisms, e.g. inducing VEGF and enabling nitric oxide (NO) production.

- There is some evidence to suggest that wounds that receive adequate oxygen generally heal at an increased rate compared to those which don't have an adequate oxygenation. However, there is uncertainty about the clinical effectiveness of such devices as reflected by the lack of reimbursement in the US.

EPIFLO SD

The device consists of a small, silent, disposable, oxygen concentrator and a 60-inch sterile cannula (tube). It can be used with any fully occlusive sterile wound dressing to continuously blanket the wound with near 100% oxygen. The patient is free to ambulate while being treated 24 hours per day for 7 or 15 days (two formats available). The company claims oxygen blanketing the wound helps metabolically energise cells to form collagen, granulation tissue, new blood vessels and skin.

Oxygen Therapy: Oxyzyme

- The product uses advanced biochemistry to work like a molecular pump, drawing-in oxygen from the atmosphere and transporting it to the surface of the wound.
- The device has two components: (i) a hydrogel sheet containing glucose, which is placed directly onto the wound; and (ii) an enzyme sheet that contains glucose oxidase. The biochemistry is triggered when the enzyme sheet is placed on top of the glucose-containing gel. Atmospheric oxygen at the surface of the enzyme sheet is trapped by the glucose oxidase and converted to a low level of hydrogen peroxide. This creates an oxygen gradient that allows more oxygen to be drawn into the dressing. The hydrogen peroxide is freely soluble in the aqueous medium of the dressing (unlike oxygen) and can readily diffuse to the interface of the dressing and the wound, where it is instantly converted back to oxygen before reaching the cells of the wound bed.
- Some of the hydrogen peroxide also reacts with iodide within the dressing to produce a small amount of iodine and dissolved oxygen. Any residual hydrogen peroxide is converted instantly to oxygen at the wound surface, and iodine has long been known for its antibacterial properties, and helps to produce an environment that is hostile to bacteria.
- OXYZYME has been developed by Insense, a privately owned, UK-based biotechnology company.

Ultrasound

- Ultrasound may be used for a number of therapeutic applications and has been used for sometime in sports medicine, diagnostic imaging and fetal monitoring. This technology is now being applied to debridement with companies such as Celleration (MIST therapy) and Misonix (SonicOne) developing these systems.

SonicOne®
Ultrasonic Wound Care System

- Wound healing progresses optimally on a wound bed clean of devitalised tissue and with controlled bacterial levels.
- This device ultrasonically fragments the necrotic tissue from the wound bed and non-migratory cells from the ulcer edge. Irrigation at the probe tip enables the tissue to be flushed from the site.
- The system is effective for the removal of necrotic tissue and fibrin while sparing the viable tissue underneath since the tissue is removed from the top down.
- Unlike other forms of debridement, the physician can easily distinguish tissue types and stop debridement when the viable tissue bed is reached.
- Vibrates at frequency of 22.5 kHz, which results in formation and collapse of vapour bubbles at the radiating surface of the probe, termed cavitation. This results in the rapid and effective fragmentation and emulsification of necrotic tissues in direct proximity to the probe.

Pulsed Radiofrequency Energy Therapy

REGENESIS BIOMEDICAL

- The Provant Wound Therapy System is an FDA-cleared medical device that aids treatment of the inflammatory responses associated with wound healing in acute post-surgical wounds and chronic wounds following debridement.
- The system is based on Regenesis' proprietary Cell Proliferation Induction (CPI) technology platform, which uses a radiofrequency stimulus to stimulate dormant cells, causing them to release natural growth factors and gene expression products that facilitate reduction of the pain and oedema associated with post-operative wound healing.
- A dosage-controlled biosignal induces expression of hundreds of genes involved in all phases of wound repair, including genes controlling inflammation responses, granulation, matrix formation, vascularisation, epithelialisation and remodelling. This stimulates the secretion of over 80 growth factors and other molecules regulating cell growth. In response, macrophages, fibroblasts, epithelial cells and myofibroblasts are induced to replicate at twice their normal speed. A 50% increase in epithelial cells and doubling in number of fibroblast has been observed following a single treatment.
- The device is compact, lightweight and portable. Treatment is twice daily for 30 minutes, and is administered by placing the applicator adjacent to the wound and activating the automatically dosed and timed system.
- However, the broader implications of accelerating cell proliferation must be considered.

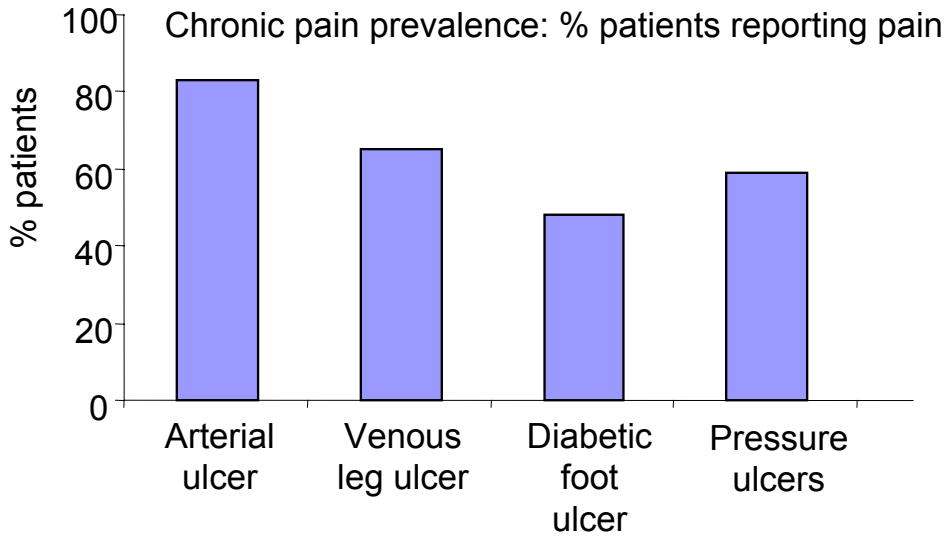
Commercial Activity

Company	Ultrasound	E-stim	Magnetic	Negative pressure	Oxygen delivery	Light/laser	Other
Anodyne Therapy LLC						X	
Biofisica		X					
Biolight International						X	
Celleration	X						
Diapulse		X					
Heatwave technology						X	
KCI				X			X
LifeWave		X					
Longport	X						
MedFaxx	X	X	X				X
Ogenix					X		
Perry Baromedical					X		
Roho							X
Regenesis Biomedical, Inc.	X	X	X				
Rich-Mar	X	X					
Romaine		X					X
Sechrist					X		
Smith & Nephew		X		X			
Thor						X	

Emerging Technologies: Addressing Pain

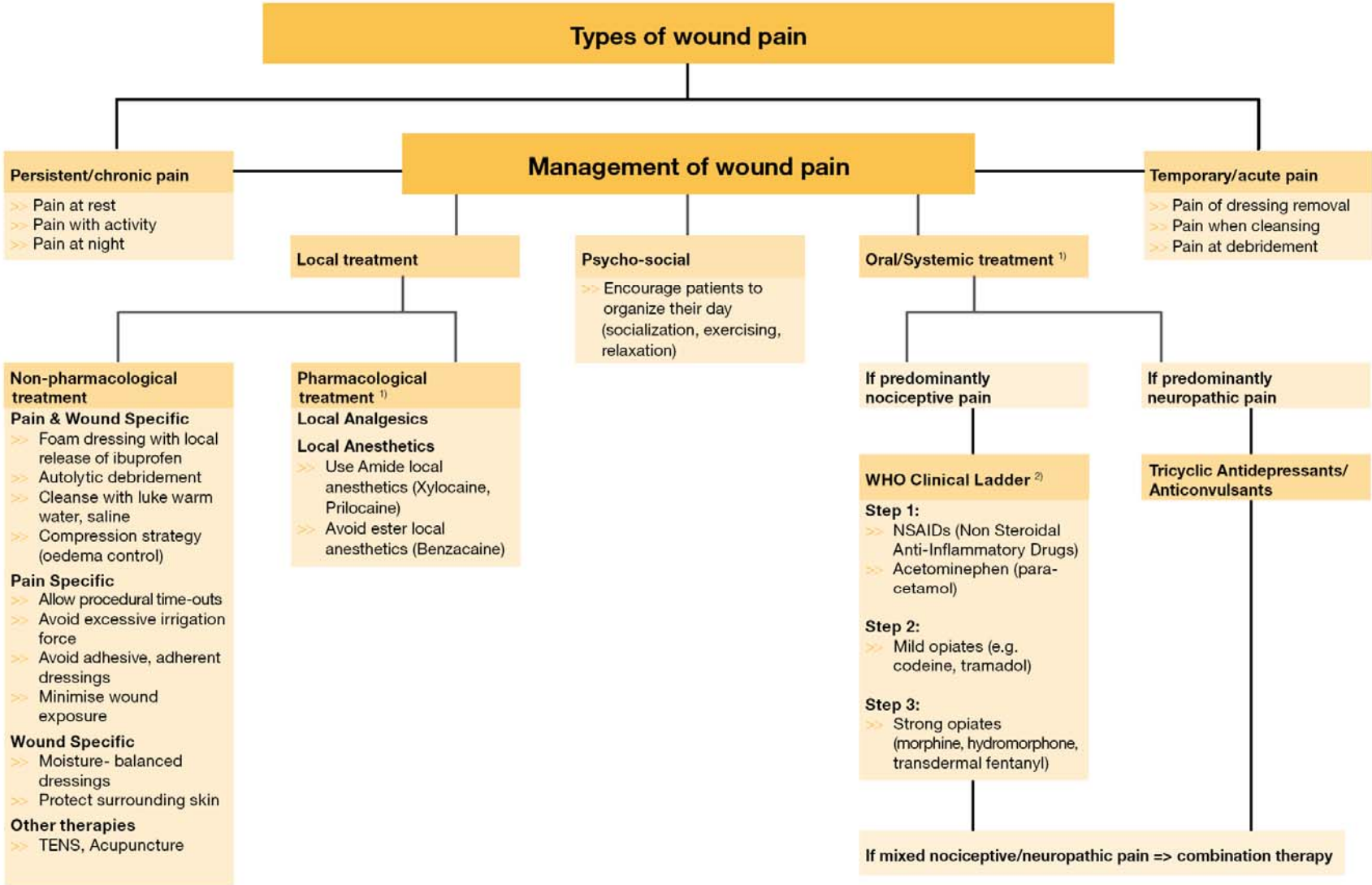
Addressing Pain

- Chronic wounds are persistently painful; 80% of patients with a chronic wound report pain at all times. 60% of venous ulcer patients report pain at levels of 'horrible' or 'excruciating'. Unsurprisingly, pain is reported to be directly and inversely related to quality of life and often dominates patient's lives.



- Wound-related pain can be classified as either: (i) temporary/acute pain, which the patient generally experiences on dressing removal, at cleansing or at debridement; or (ii) persistent/chronic pain, which the patient experiences at rest, with activity or at night.
- Persistent inflammation (a key feature of chronic wounds) triggers the release of mediators activating local pain receptors resulting in enhanced sensitivity of the surrounding skin and deeper structures in the wound base. Nociceptive pain (an aching or throbbing pain) is stimulus dependent and usually invoked by tissue damage. In contrast, neuropathic pain (a burning or shooting pain) occurs spontaneously as a result of nerve tissue damage. Most chronic wound pain is a combination of both pain types.

Current Pain Treatments



Innovation Potential: Chronic Pain

- Pain management of chronic wounds has largely been neglected. Pain relief is an emerging and potentially significant market opportunity and many view this area as having the potential to be a new therapeutic class of dressings.
- A few companies are now beginning to address this opportunity marketing dressings with in-built pain relief targeting chronic pain. However, practitioners have expressed a need for better agents with reduced adverse effects and improved delivery characteristics (sustained release and stability).

Coloplast

- **Biatian-Ibu** continuously releases ibuprofen directly into the wound and manages the pain locally instead of systemically. Pain is reduced both while wearing the dressing and during the dressing change, for up to 7 days.
- This is an example of a new product emerging from a combination of known components, the development of which has been driven by a growing clinical need.
- Some researchers were concerned that dampening inflammation may have a negative impact on wound healing. However, early studies would suggest that healing rate is not adversely affected.

ACTIVA HEALTHCARE

- **ActiFormCool** is a sheet hydrogel that works by exerting a cooling effect that provides pain relief while hydrating dry tissue.
- The temporary drop in temperature cools and soothes irritated skin, bathes the nerve endings, allows easy removal from wound. The pain relief effect lasts as long as the dressing remains in place because the nerve endings are occluded and bathed.
- However, warming of the wound bed is believed to accelerate wound healing. There is a concern that lowering the temperature will slow the wound healing process.

Innovation Potential: Acute Pain

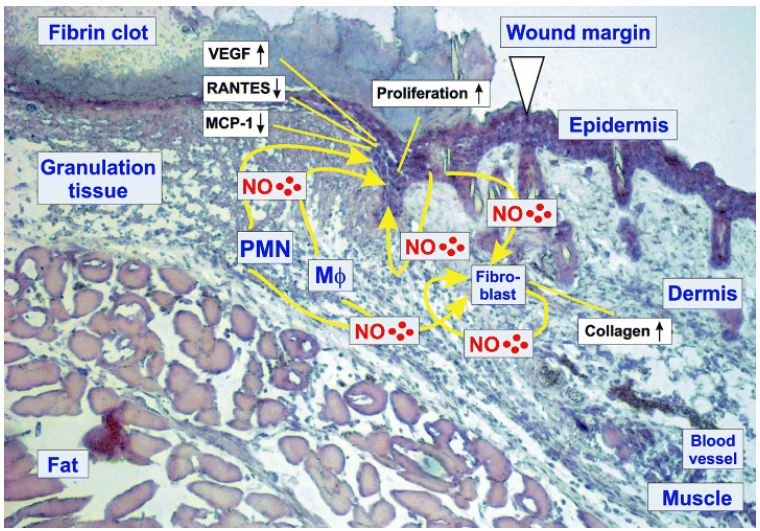
- Targeting acute pain, such as that associated with dressing change or with debridement, is also a potential market opportunity. Dressings with low-tack adhesives have been designed to reduce pain on removal. Several companies are developing technologies that address pain on debridement.
- Surgical debridement is frequently the method of choice. Tissue is cut away with sharp instruments until the wound starts to bleed. Unsurprisingly, this is a painful procedure and often requires some degree of anaesthesia. Enzymatic, chemical and biological debridement techniques are also known to be painful. Serial debridement is often required and success of this and other debriding techniques can be limited by patient intolerance to the painful procedure.
- This market opportunity is starting to be addressed with the use of ultrasound-assisted wound therapy by companies such as Arobella Medical (Qoustic Qurette), Misonix (SonicOne) and Celleration.

- Celleration has developed the MIST Therapy System, which produces a low-energy, ultrasound-generated mist that promotes wound healing through wound cleansing and maintenance debridement by the removal of yellow slough, fibrin, tissue exudates and bacteria.
- The system is a painless, non-contact, ultrasound device that has a short treatment time. The MIST Therapy creates ultrasound waves that produce and propel a gentle mist of sterile saline to the wound bed. This resulting mist of saline improves the transfer of ultrasound from the device to the wound bed without contact or pain to the patient.
- MIST Therapy also claims to promote wound healing through cellular stimulation and removal of bacteria from the wound.

Emerging Concepts:
Nitric Oxide & Homocysteine

Nitric Oxide & Homocysteine

- There are a number of new wound healing concepts that may form the basis of future opportunities. Two of these, biofilms and metalloproteinases, have already been discussed earlier in this report. However, there is an additional emerging concept in this field that has not been flagged, which relates to nitric oxide balance.
- Nitric oxide (NO) is believed to be a pivotal molecular target and intracellular signal for normal wound healing. Deficient wound NO bioactivity is thought to be a significant contributing factor for impaired wound healing in diabetes.
- Recent studies have shown that incidence of successful chronic wound closure in patients receiving specialised wound treatments (such as Regranex and Dermagraft) is positively related to the baseline threshold value of wound fluid nitrate and nitrite. Non-responders have lower levels of nitric oxide that those that respond to advance therapies. Intriguingly, homocysteine, which is a significant inhibitor or NO bioactivity, has also been shown to be elevated in non-responders. This may offer novel therapeutic and diagnostic opportunities.

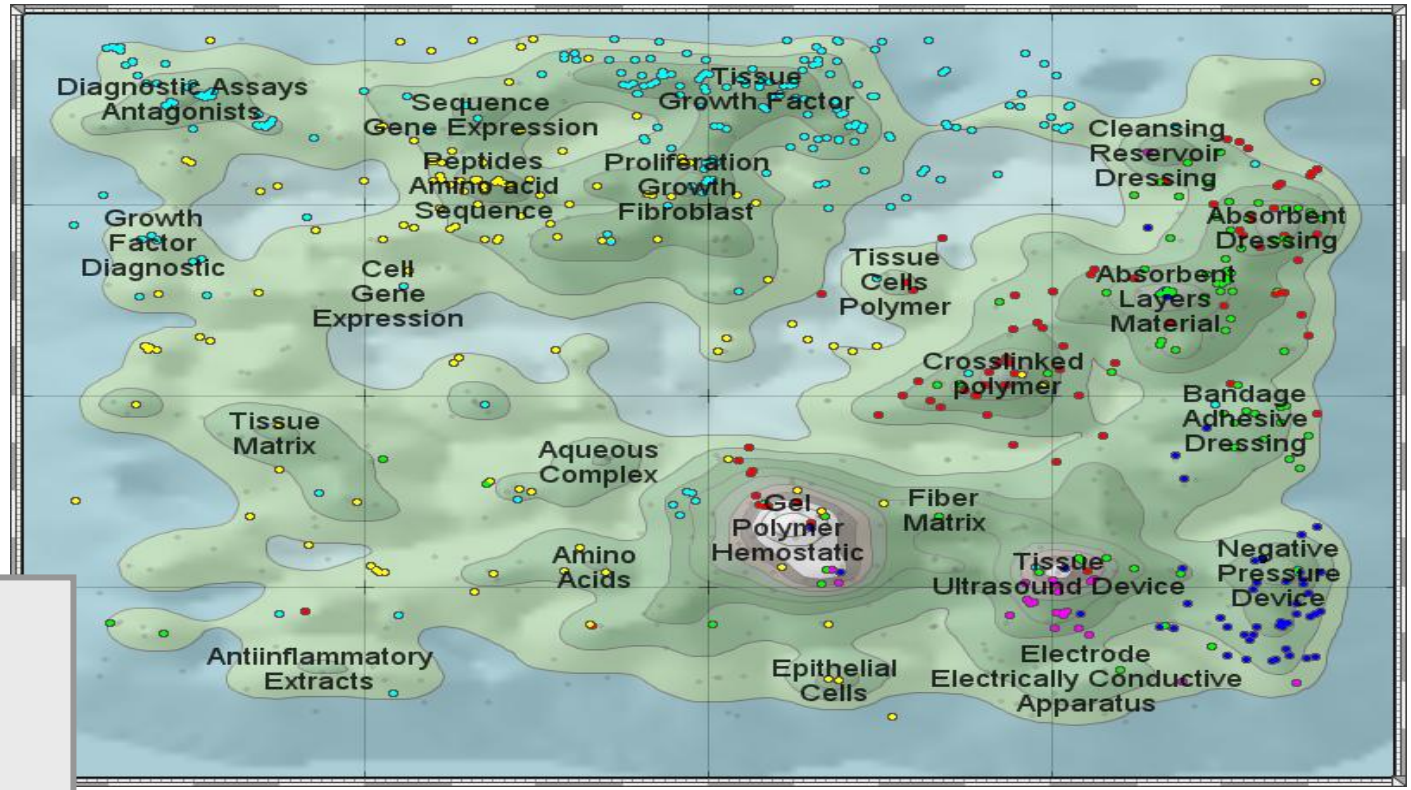


The gaseous molecule NO serves as a mediator that regulates gene expression and proliferation in keratinocytes, and collagen synthesis in fibroblasts.

[MCP-1, macrophage chemoattractant protein-1; RANTES, regulated upon activation, normal T-cell expressed and secreted; VEGF, vascular endothelial growth factor]

Patent Landscape

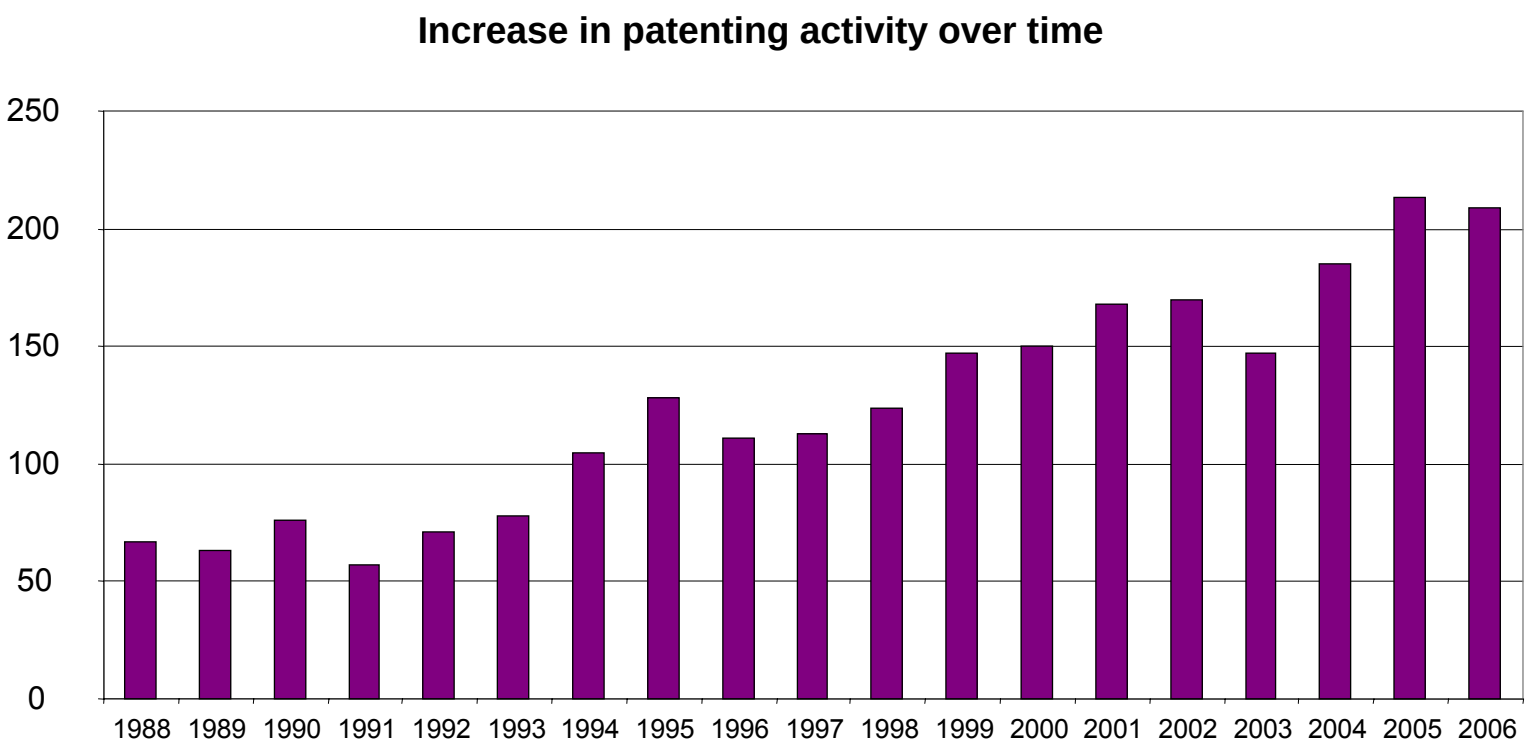
Wound Care Patent Landscape



- Moist dressing
- Advanced dressing
- Negative pressure
- Ultrasound
- Peptides
- Growth factors

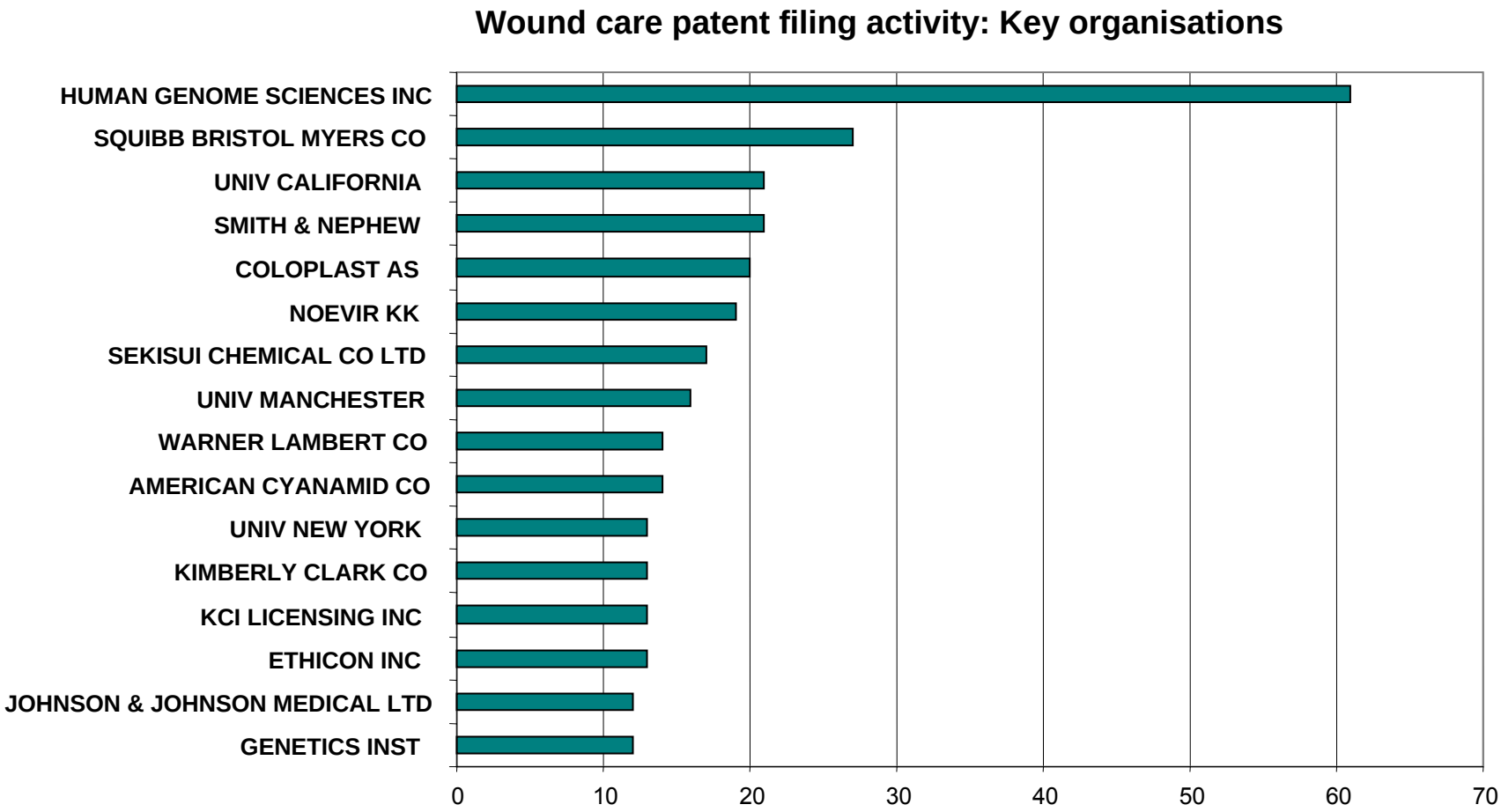
Keywords within an identified set of patents and patent applications in the field of wound healing are grouped into topics to produce a ‘map’. Collections of documents that share common elements are geographically close together whereas collections with less similarity are further away. The patent landscape is therefore displayed as a series of technology 'mountain tops' and ‘valleys’ with the higher ‘mountains’ representing the larger patent collections.

Wound Care Patent Landscape



- Search strategy: (Wound* or burn*1 or (diabetic adj ulcer*)) near2 (heal* or care or repair* or manag* or treat* or application) in title or abstract. This produced 2517 hits.
- It is interesting to note the slow incline in patenting activity over time and the cyclical nature of the rise.

Patent Filing Activity



- Over 900 organisations or individuals have filed patents in this area, many hold single patents.

Subanalysis

- The wound care patent database was subanalysed to assess patent activity relating to the emerging technologies.
- Technologies were placed into four subgroups as outlined below. A total of 1545 patent families were included in this analysis.

Subgroup 1: Infection control

- Antimicrobial peptides
- Biofilms

Subgroup 2

- Biologics
- Gene therapies

Subgroup 3

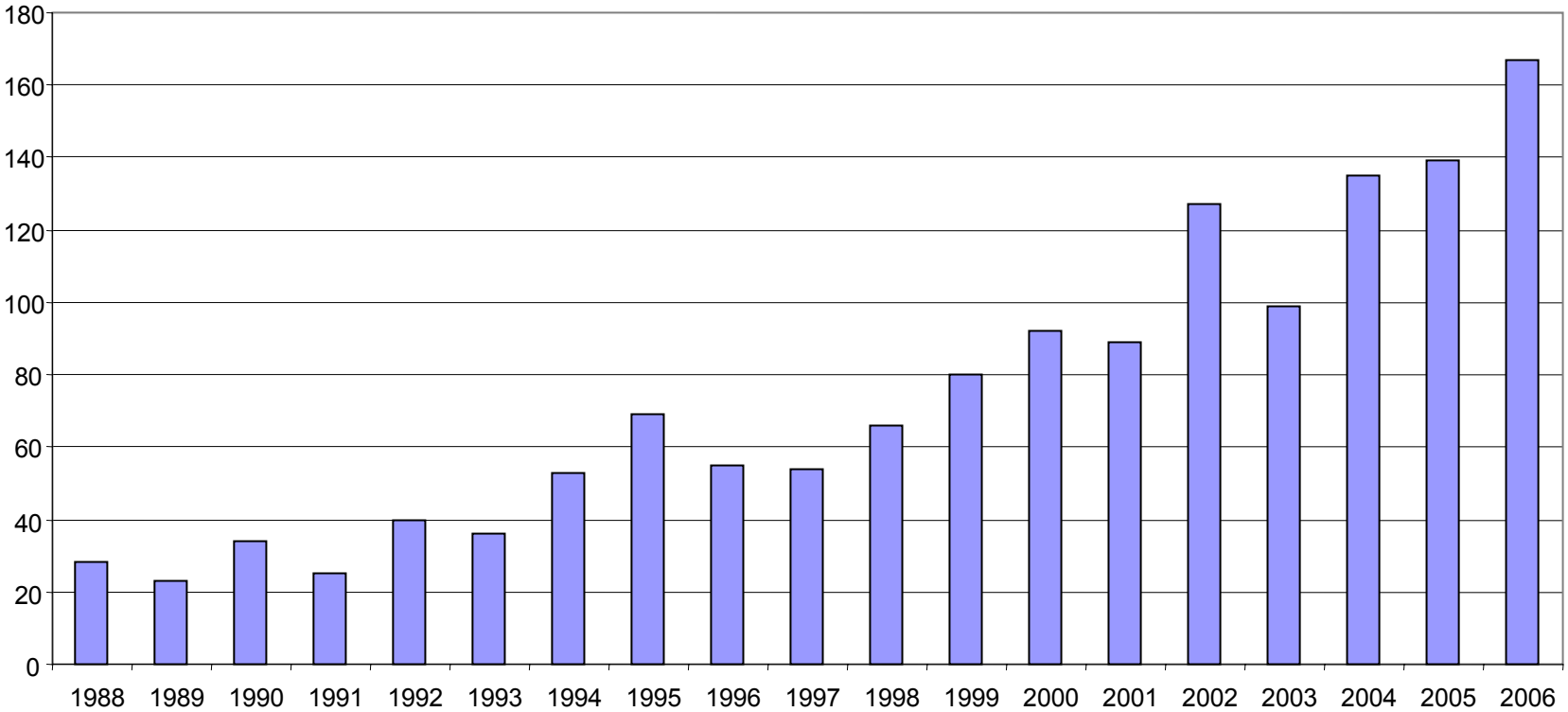
- Skin substitutes
- Scaffolds
- Bioactive materials
- Sealants
- Stem cells

Subgroup 4: Physical therapies

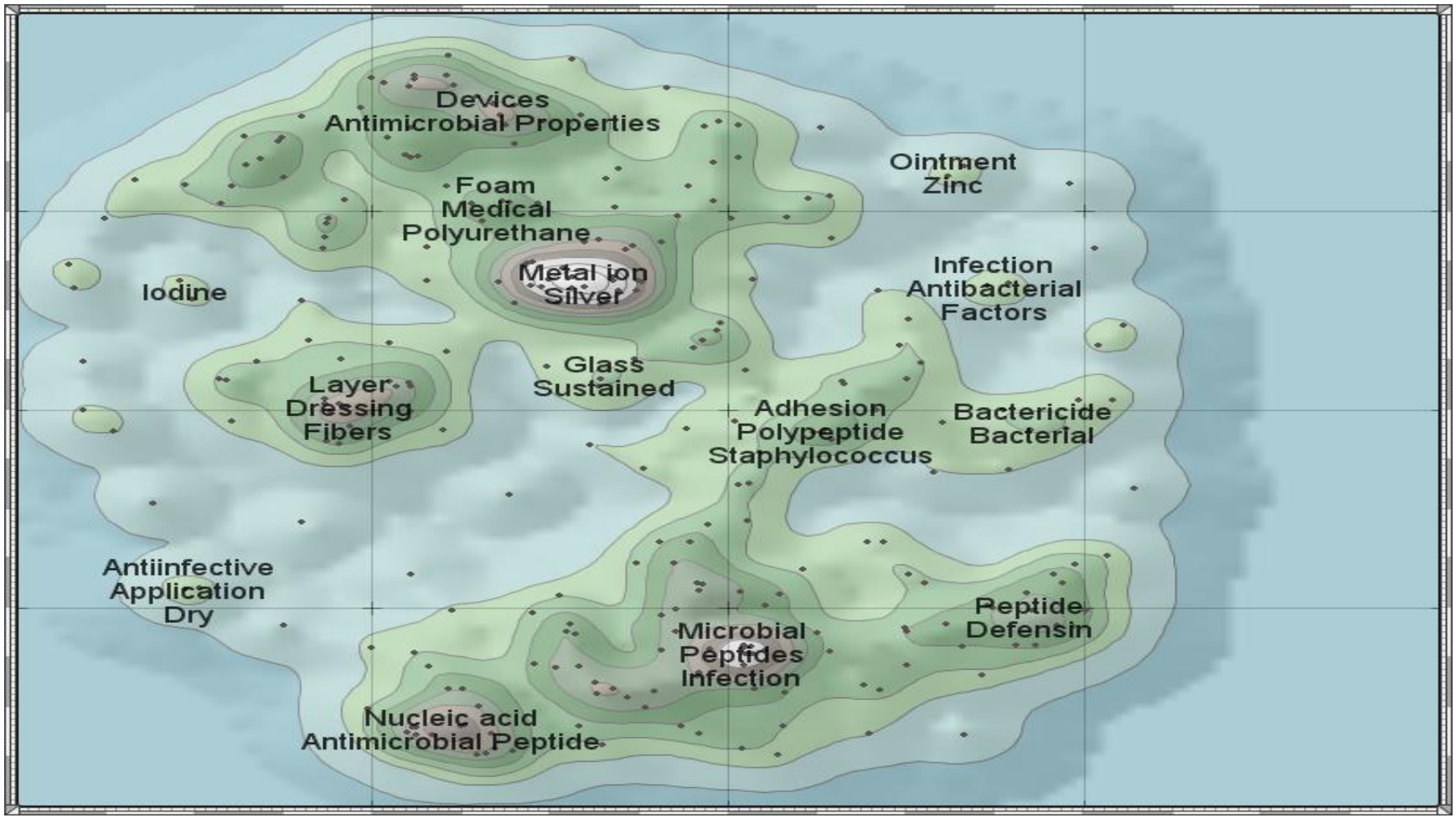
- E-stimulation
- Light/laser
- Ultrasound
- Oxygen

Subgroup Analysis: Patenting Activity

Increase in patenting activity over time for all four subgroups

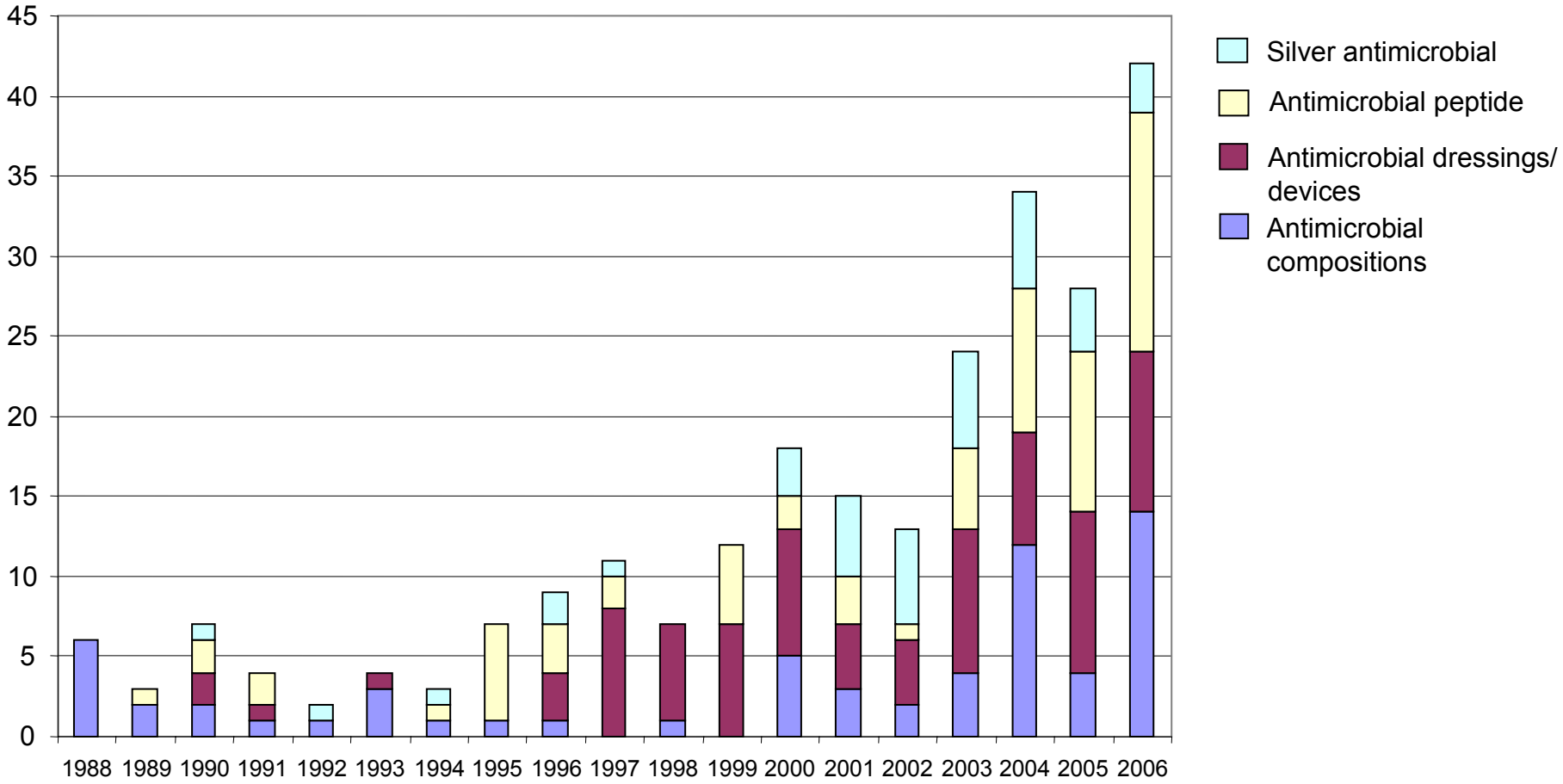


Antimicrobials patent landscape



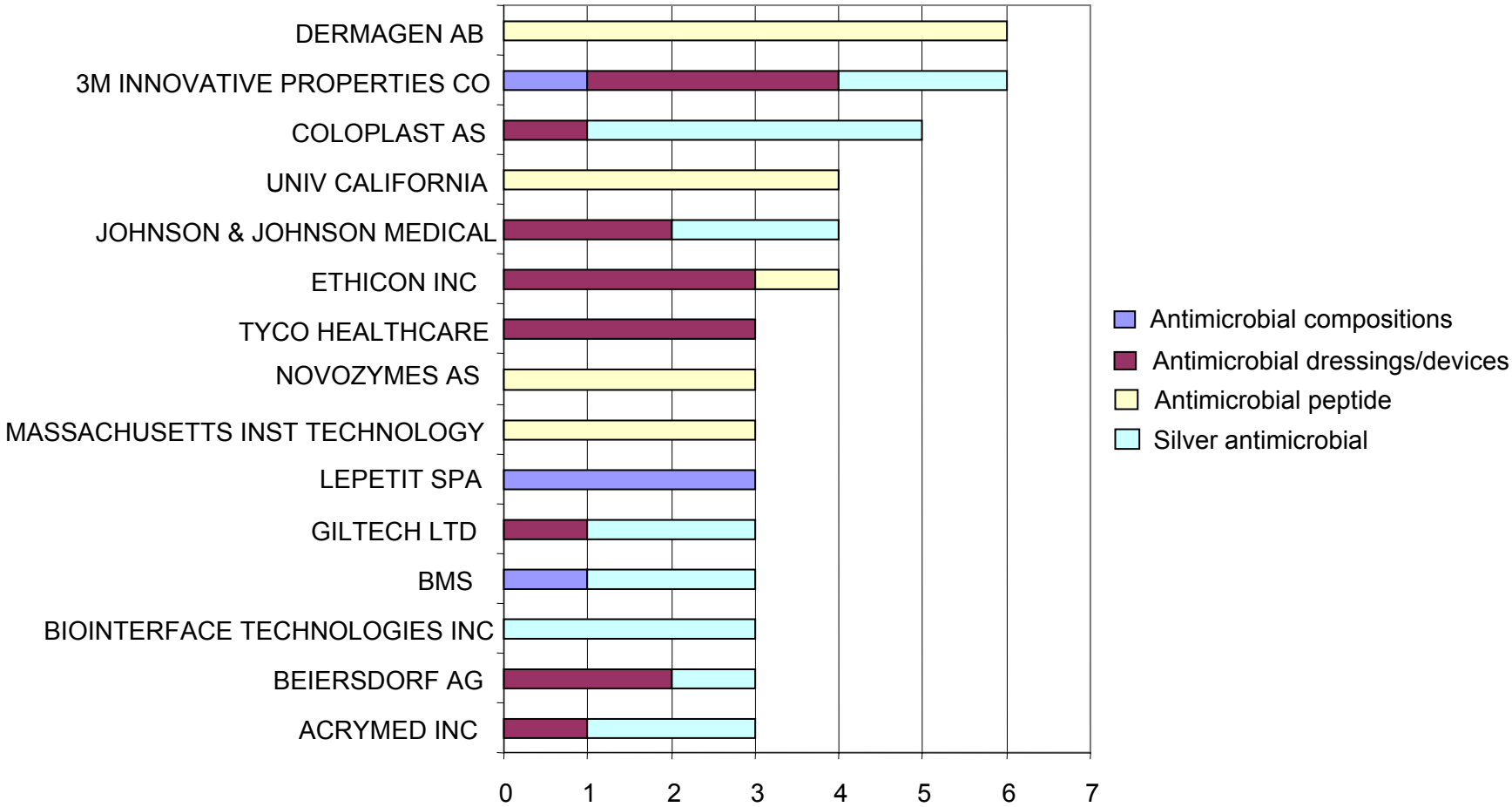
Antimicrobials

Patent activity over time and category distribution

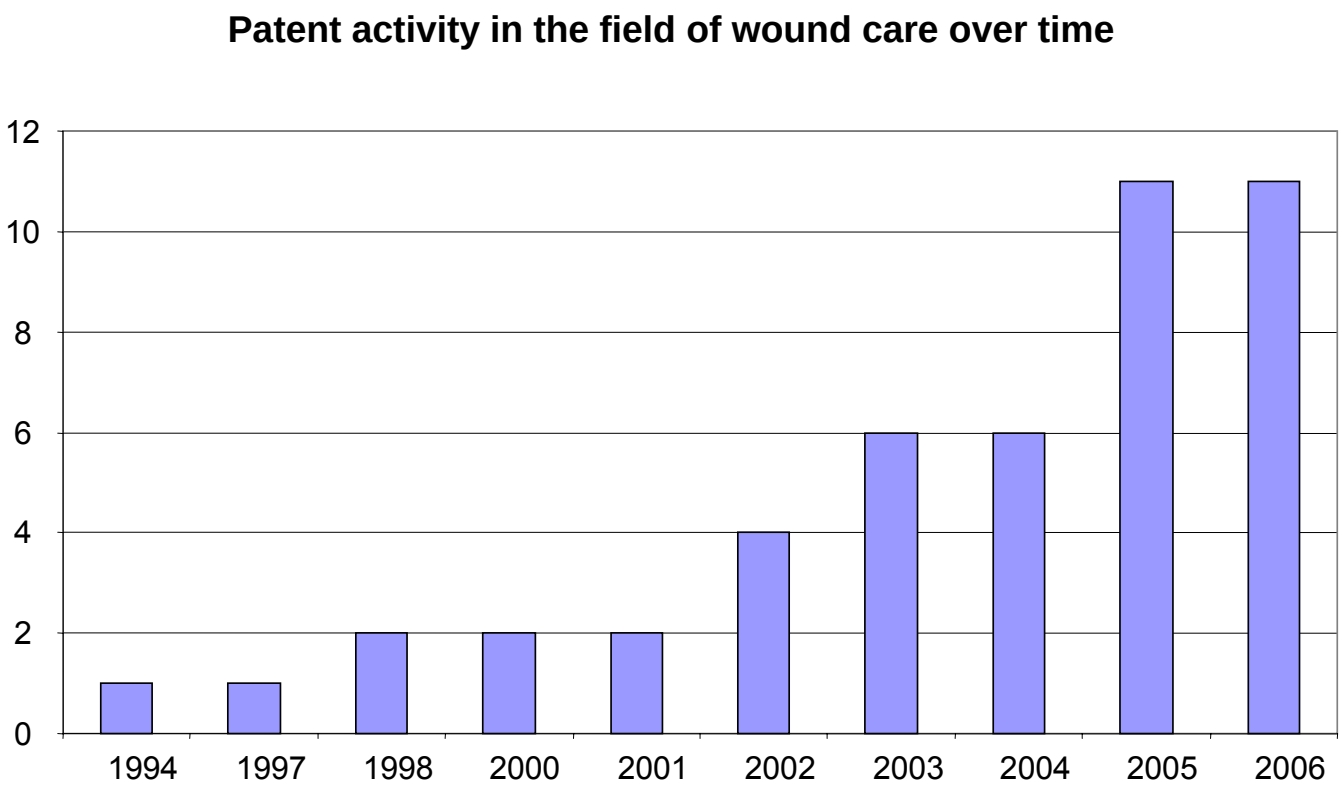


Antimicrobials

Antimicrobials patent filing activity: Key organisations



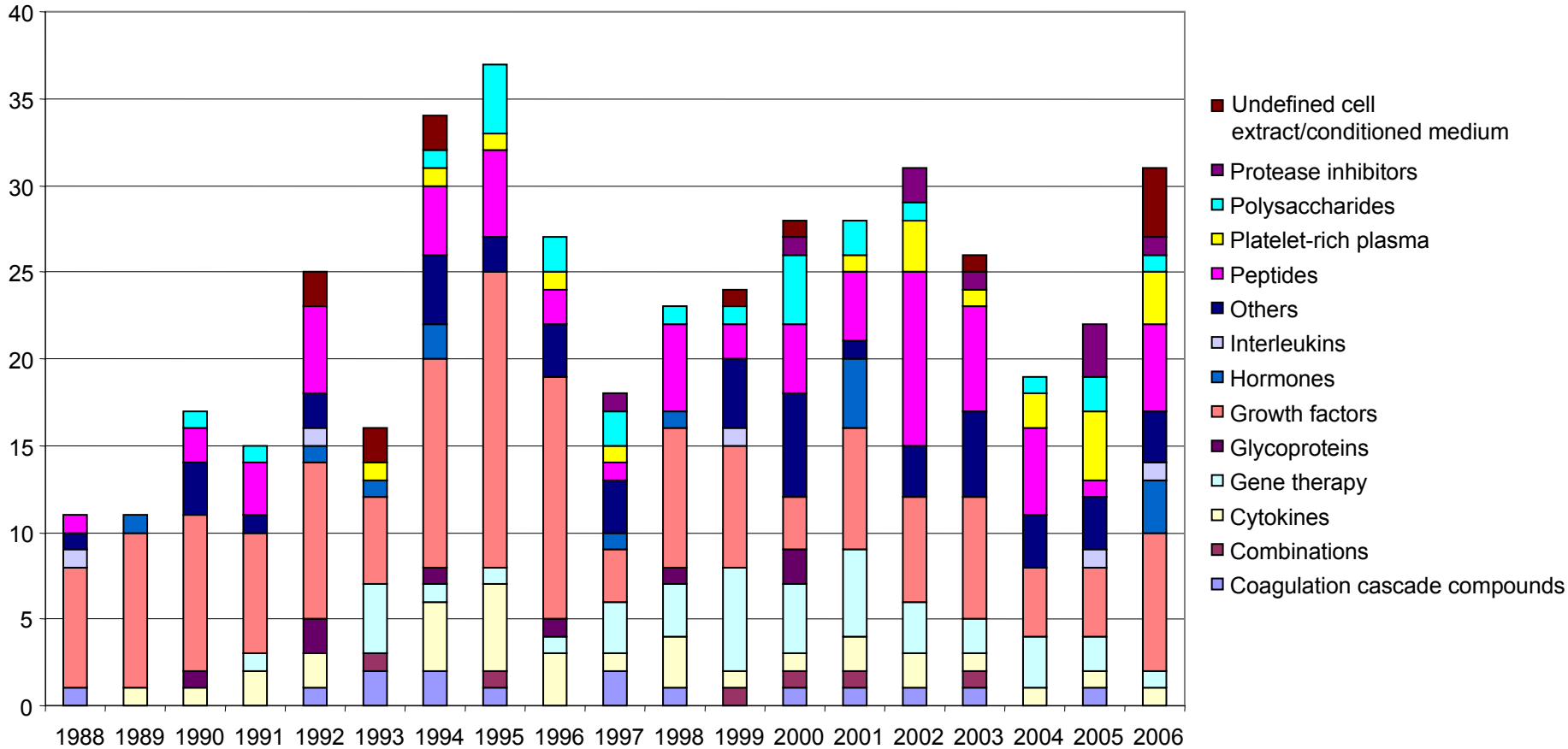
Biofilms



- Only two companies hold more than one patent in this specific area: Kane Biotech, Inc. and MBEC Bioproducts.

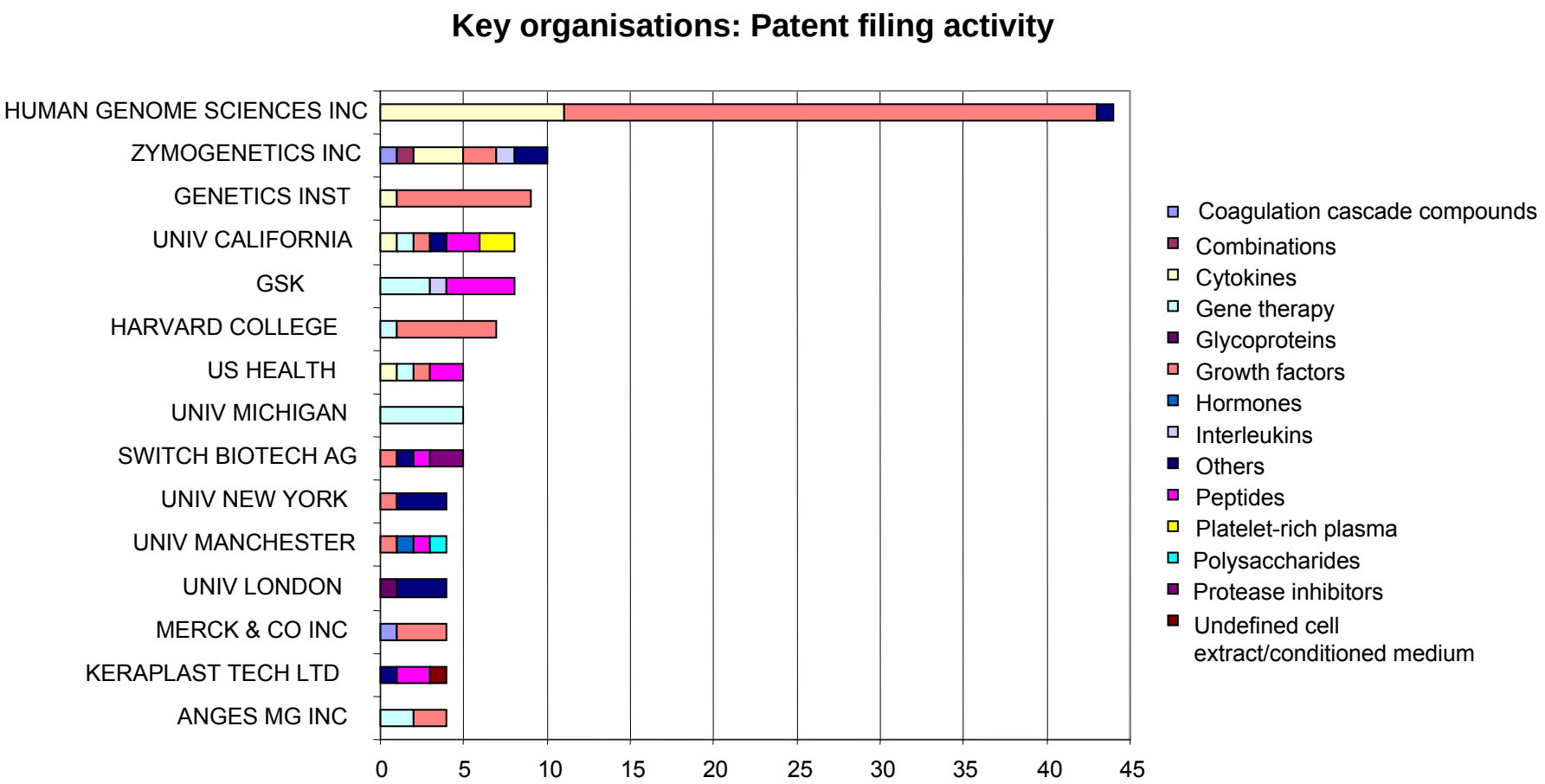
Biologics & Gene Therapy

Patent activity over time and category distribution

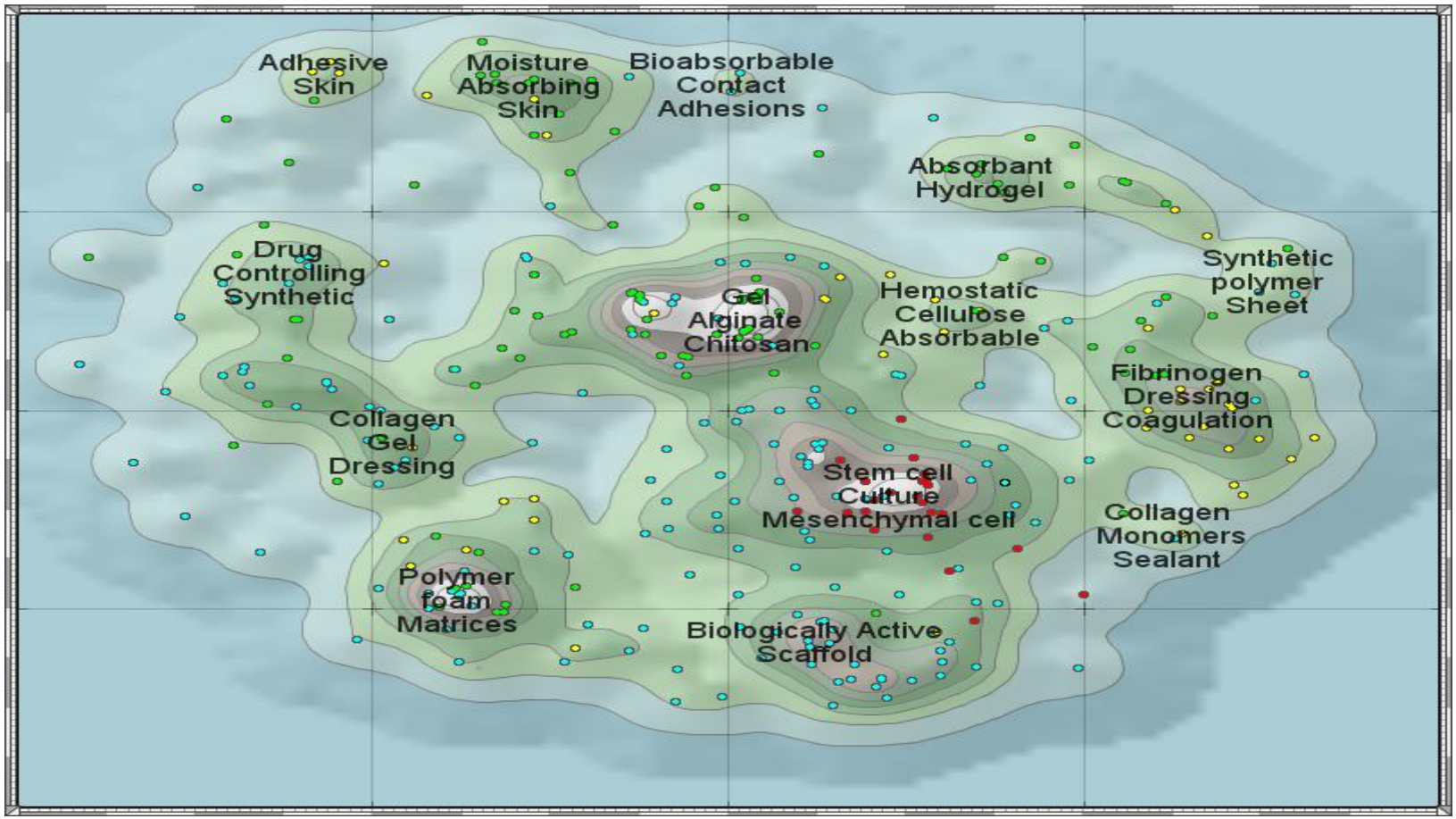


- 462 patent families were included in this analysis.

Biologics & Gene Therapy

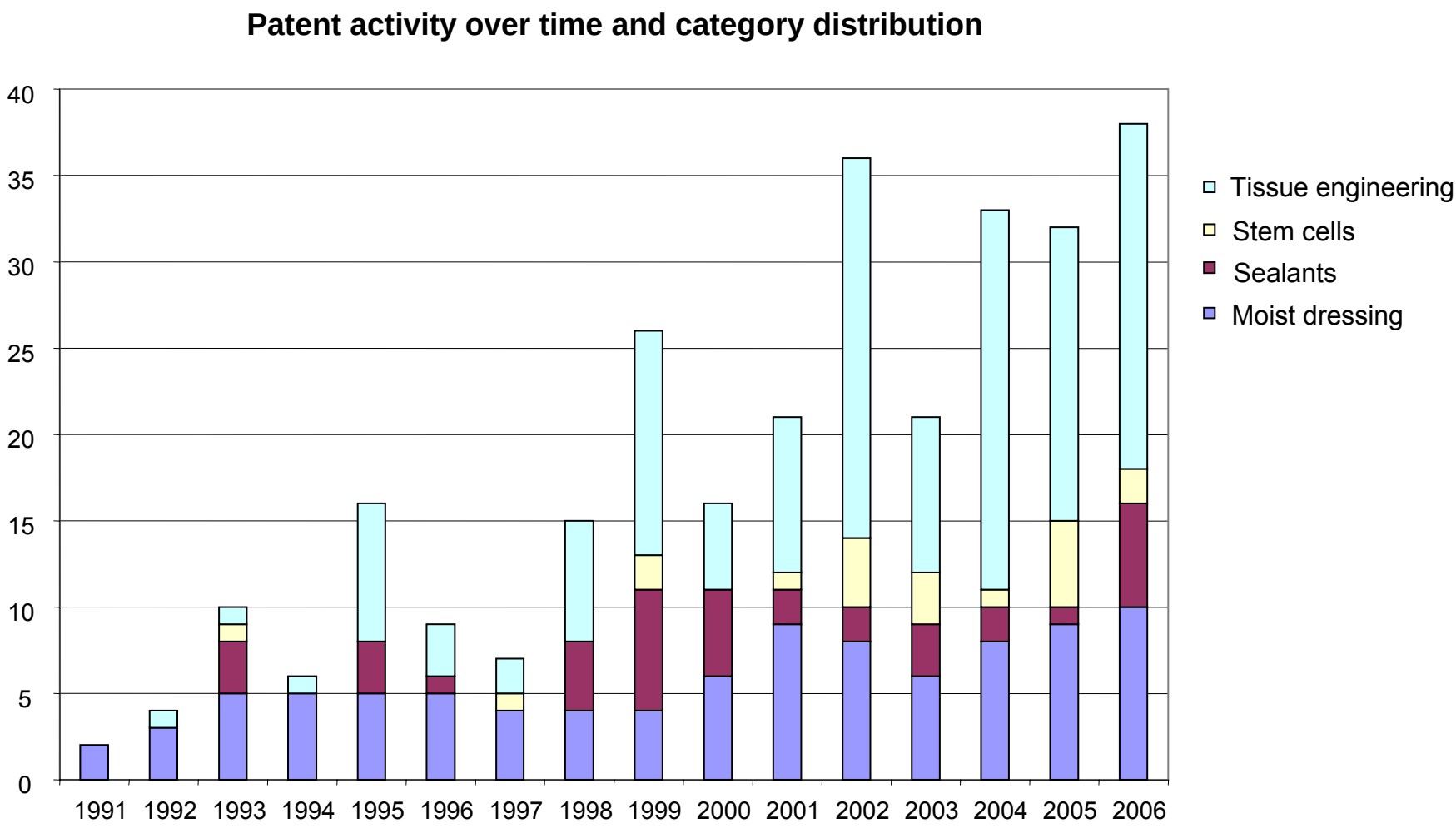


Skin Substitutes *et al.*



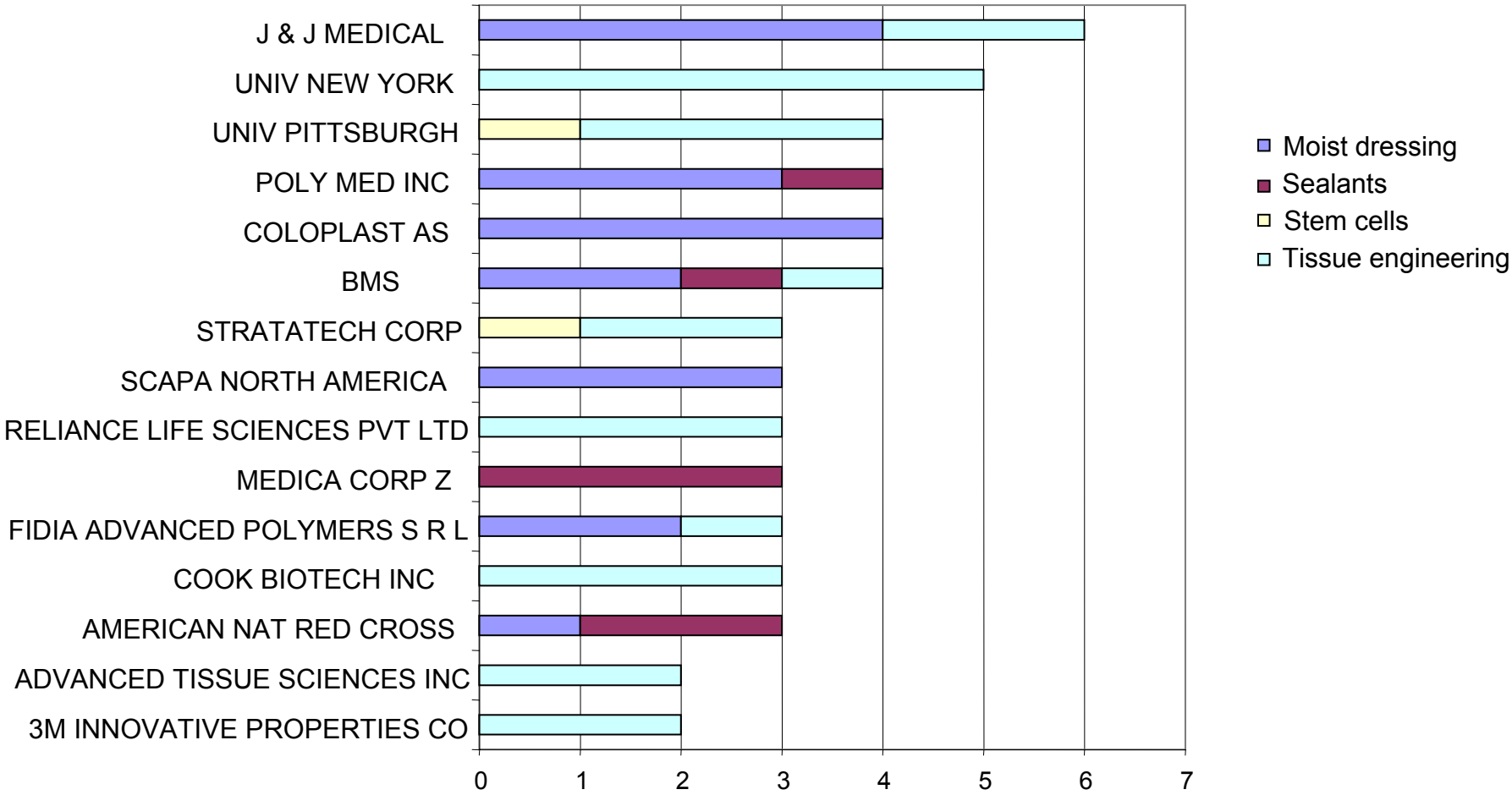
- This subgroup included moist dressings, active biomaterials, scaffolds, skin substitutes, sealants and stem cells. 338 patent families were identified and included in this analysis.

Skin Substitutes *et al.*



Skin Substitutes *et al.*

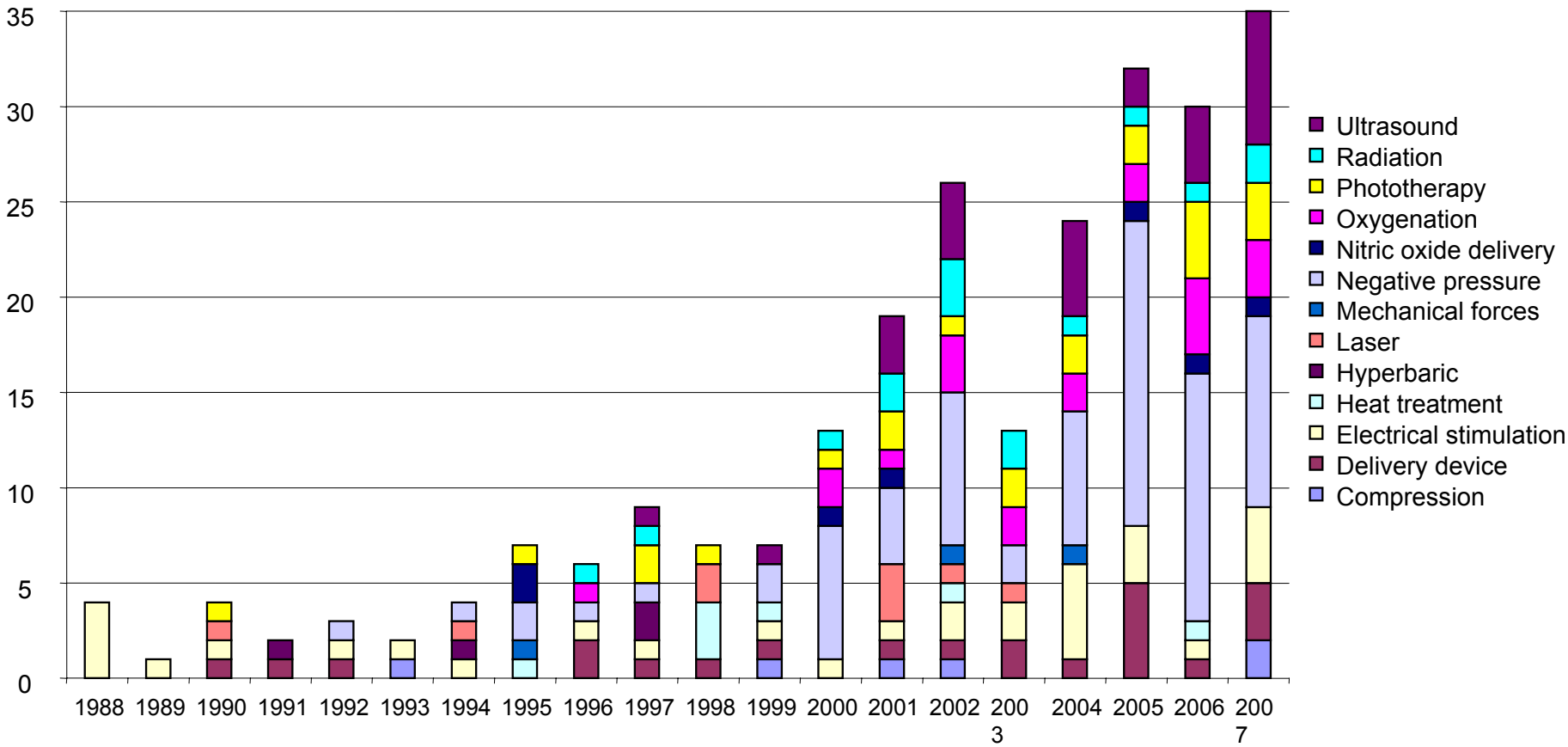
Key organisations: Patent filing activity



Physical Therapies

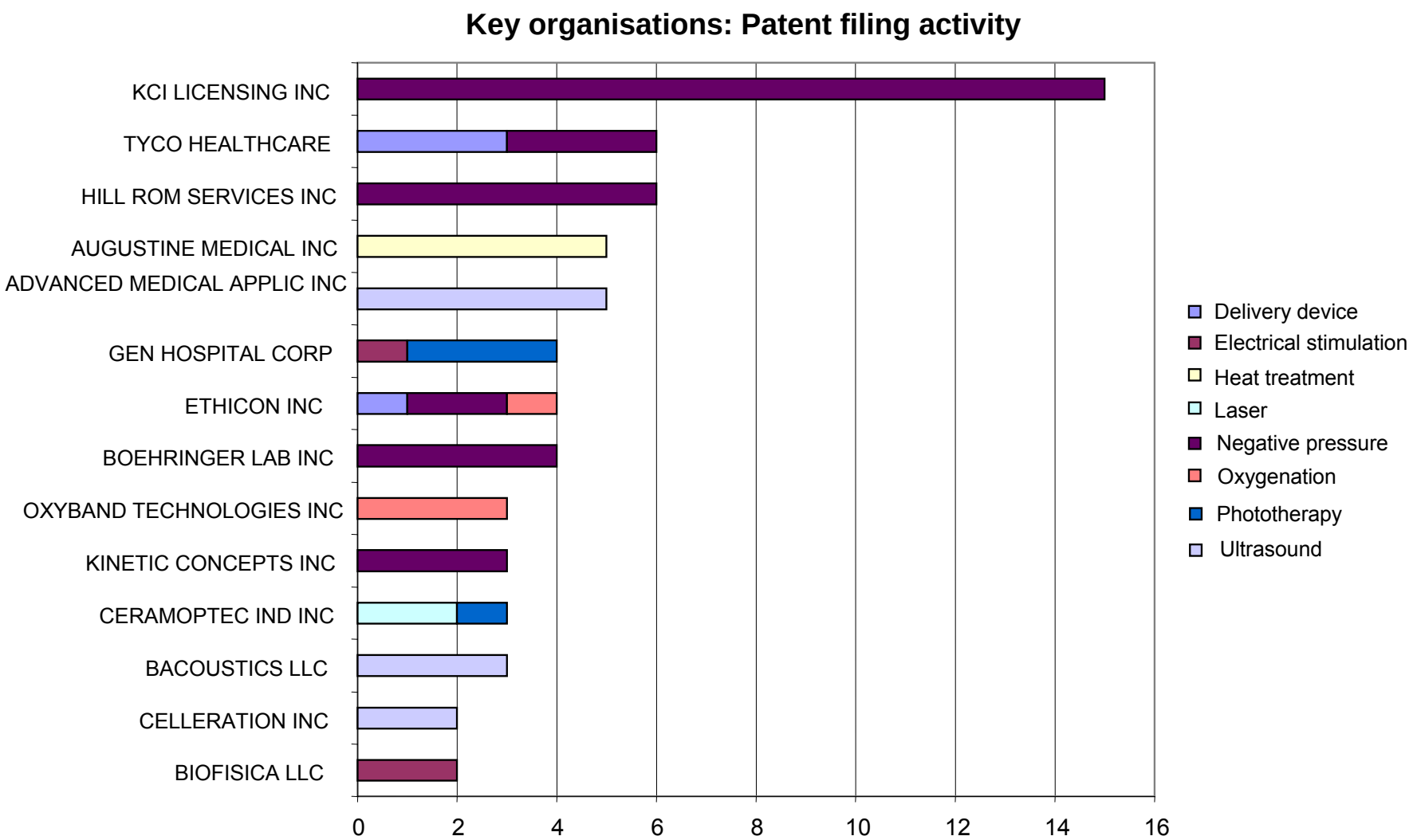
Physical Therapies

Patent activity over time and category distribution



- 257 patent families were included in this analysis. Data from 2007 are included to illustrate the growing patent activity in this area. Given the significant delay between patent filing and visibility, these data represent filing activity in the early part of 2007 only.

Physical Therapies



Scottish Activity

Scottish Activity

Infection control

Research:
- Strathclyde (novel antibacterial technologies and compounds)
- Strathclyde (infection diagnostic)
- Edinburgh (antibacterial peptides)
- Dundee (biofilms)
- ROLEST (electronic sterilisation technologies)
- Aberdeen (antibacterial peptides)

Commercial:
- Novabiotics (antimicrobials)
- Aquapharm (antimicrobials)
- Dimensional Imaging (surface imaging)
- Wallace Cameron (UV disinfectant)
- Amoebics (antimicrobials)

Nitric oxide

Research:
- Edinburgh (action)
- St Andrews (delivery)

Scaffolds

Research:
- Dundee (scaffolds and tissue engineering)
- Aberdeen (scaffolds)

Commercial:
- Giltech (controlled release scaffolds)
- Burdica (hyaluronic acid)
- Controlled Therapeutics (hydrogel delivery)
- BioFilm (thin films)
- Hyaltech (hyaluronan)
- Mentor Biopolymers (hyaluronan)

Clinical expertise
- Scottish Infection Research Network
- Leg Ulcer Forum Scotland
- Tissue viability clinics (Aberdeen, Glasgow)
- Dermatology (Edinburgh)

Physicals therapies

Research:
- Aberdeen (electrical stimulation)

Commercial:
- Lumicure (light-based therapy)
- Divex (hyperbaric)

Materials

Research:
- Heriot-Watt (Biomedical Textiles Research Centre)

Commercial:
- Ethicon/Johnson & Johnson
- Culzean Medical Devices (fabric)
- Second Skin (customised compression dressings)

Others

Biologics: Dundee (novel growth factor)

Pain management: Edinburgh (neuropathic)

Conclusions and Opportunities

Conclusions

- There are many wound types but chronic wounds, such as diabetic ulcers and venous leg ulcers, are potentially the most attractive therapeutic target due to the growing patient pool, their lengthy time to heal and the need for improved advanced technologies.

- Indeed, the wound care market is seen to be experiencing a shift from traditional dressings to advanced wound dressings as clinicians strive to increase the number of healed chronic wounds and decrease their healing times.

- The biggest challenge facing companies developing such technologies lies in the ability to balance the need for typically high-technology products that stimulate the healing process with budgetary healthcare pressures. There is now mounting pressure for companies to demonstrate the cost effectiveness as well as efficacy of their products. This, together with the increased regulatory requirements of the more advanced products, significantly impacts development costs.

- Skin substitutes are an example of one product category that have suffered from these pressures. The road to market introduction for many of these manufacturers has been fraught with clinical and financial disappointments due to poor clinical trial results, funding difficulties and the high cost of development with the corresponding low profit margin once introduced to the market. Once on the market, companies have needed to sell these products at significantly higher prices than conventional therapies to recoup the costs, which has significantly limited growth.

Conclusions

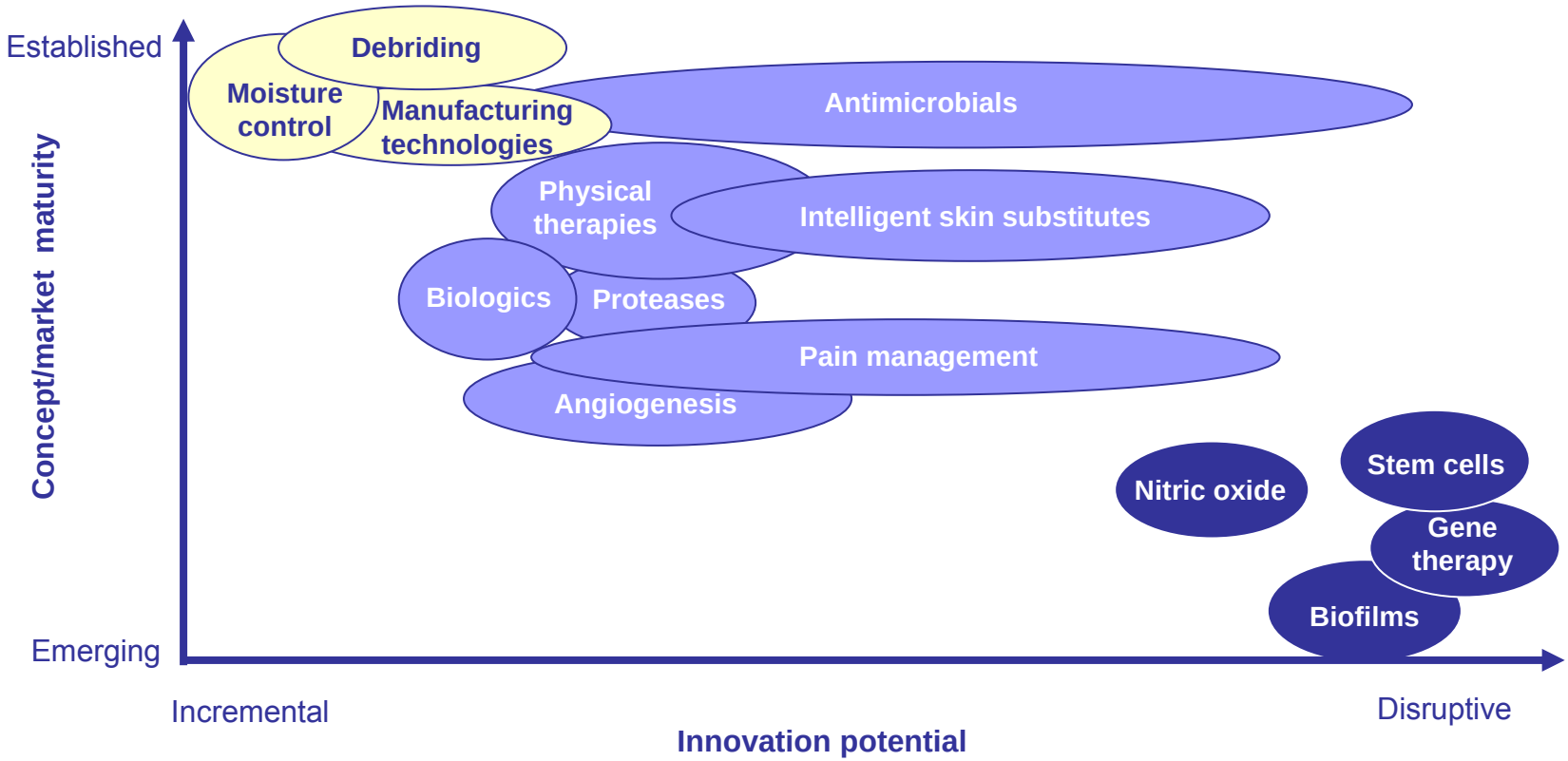
- So caution should be exerted before entering the advanced wound management market; indeed, this area has been viewed with much scepticism by venture capitalists for a number of years. This is perhaps reflected in the patent filing activity, which overall has shown slow growth and cyclical trends. Many new products are actually hybrids of existing technologies such as the moist wound dressings with antimicrobial activity recently launched.

- However, KCI has shown that it is possible to develop new and innovative technology that will succeed in this market. KCI's negative pressure wound therapy (VAC) has achieved phenomenal growth and is now a billion dollar product. The success of VAC has demonstrated the huge market potential for cost-effective, efficacious approaches.

- The success of VAC can be attributed to a number of factors. However, it is interesting to note that it enhances wound healing via a number of mechanisms. Wound healing is a complex process and a single modality is unlikely to be effective. Successful products in this sector are likely to be those that simultaneously address a number of barriers to wound healing or alternatively tackle a major barrier such as infection.

Conclusions

- This report has provided an overview of the products currently in the marketplace and also the emerging technologies, which could become the products of the future. The analysis outputs are illustrated below, positioned according to innovation potential and concept or market maturity.



Opportunities

- ITI believes that there are a number of opportunities in this area, given the market potential and innovation needs. The market potential of these opportunities, however, must be weighed against the increasingly high development costs of such products and the price sensitivity of the market.

- **Novel antimicrobials:**

  Antibiotics are commonly used to treat wound infection. However, there is increasing concern about the development of bacterial resistance to these antibiotics. Antiseptics are also used to treat infection and although resistance to these is unlikely, they are non-specific in their action and so might have toxic effects on human cells involved in the healing process. There is, therefore, a need for a new class of antimicrobial therapies that have rapid, broad-spectrum action, no toxicity issues and do not induce resistance. Several researchers believe antimicrobial peptides to have potential. Such technologies are likely to have additional applications outside of wound care.

- **Biofilm eradication:**

  Recent studies have shown biofilms to be present in the majority of chronic wounds. These are resistant to antibiotics, UV irradiation and antiseptics, and so are difficult to remove. The role of biofilms in wound healing is controversial, with some researchers now proposing biofilm formation as being the best unifying explanation for the failure of all chronic wounds to heal; others remain sceptical about their actual existence in the wound bed. This emerging area of research could offer opportunities around biofilm detection, as well as new strategies for their removal. Biofilms are also a problem common to other industries and so there are likely to be additional applications for any developed biofilm technologies.

Opportunities

- **Biologics delivery platform:**

  Growth factors are known to play a key role in stimulating the wound healing process and many companies have tried to bring related products to the marketplace. However, this sector is littered with failures with only Regranex (PDGF) reaching the market. This failure is due, at least in part, to product instability in the wound bed; they are rapidly digested by proteases and MMPs. As a result, Regranex is applied in supra-physiological doses. This has cost implications but also gives rise to safety concerns. There is an opportunity to develop delivery technologies in this space, which may enable previous biologic failures to be brought to the market.

- **Pain management:**

  Pain management of chronic wounds is a largely neglected area despite the high level of pain experienced by many patients on a daily basis. A few products have now reached the marketplace to address this need. However, there is still a need for improved therapeutic agents with reduced adverse effects (particularly in terms of slowed wound healing) and improved delivery characteristics (sustained release and stability). This area has the potential to become a new therapeutic class of dressings.

- **Optimised physical therapies:**

  A number of physical therapies have been developed and marketed as wound healing stimulators. However, the efficacy of many of these devices has been questionable and practitioners remain sceptical of the technology and slow to adopt such techniques. The mode of action of these technologies is poorly understood and, as a result, many feel the devices currently marketed are sub-optimally designed and ineffective. There may be an opportunity to optimise such technology and deliver an efficacious product. However, strong clinical trial data will be required to overcome physician scepticism and patent protection might be hard to achieve given the number of companies operating in this space.

Opportunities

- **Intelligent skin substitutes:**

  These are proposed to be the next generation of skin substitutes and will take the form of a biomaterial scaffold engineered to facilitate cell migration and adhesion. There is a need for new biomaterials with improved properties. Emergence of acellular constructs with or without synthetic backbones would lower the manufacturing costs and are predicted to drive unit volume growth. However, market size is currently small and first-generation technologies have struggled. As a result, market potential may be limited.

- **Nitric oxide balance:**

  The role of NO and, potentially, homocysteine in chronic wound healing is an emerging concept that merits further academic investigation. Strategies to measure and modify activity may offer novel therapeutic and diagnostic opportunities.

Next Steps

If you would like to discuss the report findings and related opportunities with us further, please contact ITI Life Sciences at:

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For more information on ITI Life Sciences, please visit: http://www.itilifesciences.com/

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Sources

Note: all market estimates and forecasts were provided by Frost & Sullivan unless otherwise indicated.

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