

Product Development

Wounds: Not open & shut

BioCentury This Week

Cover Story

Not Open & Shut — Wound healing fell off the radar in the 1990s after an abundance of clinical failures and poor sales for the few approved treatments. But efforts have been rekindled by proof that a massive and growing market exists, coupled with a growing compendium of knowledge about the biology of what makes wounds chronic.

Strategy

RNAi(ndependence) — Through its progression of strategic partnerships, Alnylam has preserved its ability to continue to monetize its RNA interference platform as it ripens, and especially to build its own therapeutics pipeline.[/A8](#)

Gambling on Partnerships — After abandoning in-house research, Procter & Gamble Pharmaceuticals is depending on its consumer marketing expertise to build a pipeline, an approach exemplified by its deal with Dong Wha of Korea.[/A10](#)

Green Eyeshades — Ariad maintains that holding on to the books is a key feature of its deal with Merck for the biotech's AP23575 small molecule mTOR inhibitor for cancer.[/A11](#)

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Down-Sizing the High — Catalyst is applying an enzymatic approach to control dopamine release, aiming to sidestep the side effects associated with GABA receptor agonists to treat substance abuse.[/A12](#)

Upgrading from OTC — Akesis thinks its version of vanadium will have efficacy, safety and dosing advantages over OTC formulations used to control glucose, and have a place behind metformin as a drug to treat Type II diabetes.[/A13](#)

Emerging Company Profile

Shipping Around — Aquinox is aiming to modulate new targets in the PI3K pathway, which it believes may provide the hoped-for benefits of PTEN agonists in cancer while circumventing their limitations, as well as working in inflammatory diseases.[/A14](#)

Politics & Policy

Taxing Carried Interest — Congress has taken up the argument over whether the carried interest of private venture fund partners should continue to receive capital gains treatment, or be taxed as ordinary income.[/A15](#)

Ebb & Flow

Cash Isn't Data — Alnylam's enterprise value. Drug Royalty's FluMist bet. The Street: Rodman runs a reverse; MPM BioEquities; Bank of America. Funds: Galen Partners. Analysts. Also: Dendreon; Northwest Bio; Antisoma; Depomed; Idenix; ImClone; Karo Bio; Theravance; Dyax; Noven; Qiagen, et al.[/A16](#)

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By Michael Flanagan
Staff Writer

The failure of a series of wound healing agents, combined with disappointing sales for the few products that were approved, eroded interest in the space in the 1990s. But efforts now have been rekindled by proof that a massive market exists for effective approaches, coupled with the knowledge that the medical need will only expand as the population ages and the diabetes epidemic grows.

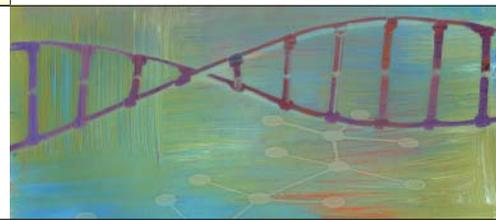
The clinical experience with some of these early agents, including topical growth factors, provided two lessons: chronic wounds are too complex to address using a single modality, and when control patients in trials received proper standard care, their wounds often healed. As a result, it was exceedingly difficult to show efficacy.

In the interregnum, researchers have compiled a more sophisticated knowledge of the biology of what makes wounds chronic. As this has become better understood, new targets have been discovered. For example, researchers recently published in the *Journal of Clinical Investigation* that stromal-derived factor-1a (SDF-1a), a chemokine mediator of endothelial progenitor cells, may play an important role in diabetic wound healing and could represent a novel therapeutic target.

In addition to promoting skin cell differentiation and migration, companies have begun focusing more attention on improving blood flow and addressing the delicate balance of localized inflammation that can both help and hinder wound

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healing.

Going back to the drawing board also has meant selecting patients for trials whose wounds don't heal even with best standard care.

Chronic mystery

A fresh wound normally undergoes a natural progression of inflammation, proliferation and remodeling that acts to keep the site free from infection while regenerating the lost or damaged dermal and epidermal tissue. Some wounds, however, do not heal. The majority of chronic wounds fall into three categories: diabetic, pressure and venous ulcers.

Diabetic ulcers are often caused by a combination of neuropathy, poor circulation and a compromised immune system. As many as 15% of patients diagnosed with diabetes can be expected to develop a non-healing wound. Pressure ulcers, or bedsores, arise as the result of pressure that cuts off circulation to the area. Venous ulcers, which are most prevalent in the elderly, develop in large part due to venous hypertension and improper valve functioning that results in ischemia and tissue damage.

Until the late 1980s, wound healing was the domain of home care, where the main products were devices and dressings that were used by nurses, according to Peter Sheehan, a senior faculty member at the Mount Sinai School of Medicine, who has served as an investigator in numerous clinical trials of wound healing agents.

"Only now are we really coming to understand some of the mechanisms behind wound healing and, in contrast, which mechanisms of wound healing may be impaired," said Sheehan.

"People traditionally focused on wound healing have been interested in skin tissue repair and regeneration, but we are learning some important lessons from other colleagues who are looking at tissue injury repair in bone and cartilage, as well as the myocardium and vascular wall, which represent a much larger group of orthopedists and cardiologists, where there is more funding available," added Sheehan.

According to Lisa Gould, an assistant professor at the University of Texas Medical Branch at Galveston, important advances in chronic wound management have been made using topical antimicrobials and negative pressure methods. However, aside from the common components of ischemia and inflammation, the underlying problem is that "we still do not understand what makes wounds chronic — why they become chronic, why they stay chronic, and how to get them out of being chronic."

First-generation products

Few products have been approved for chronic wound indications. Some of the earliest products to hit the market were Apligraf, a skin substitute from Organogenesis Inc. (Canton, Mass.) made of bovine type I collagen plus human fibroblasts and keratinocytes, and Dermagraft, a human fibroblast-derived skin substitute marketed by Advanced BioHealing Inc. (ABH, La Jolla,

Calif.).

FDA approved Apligraf to treat venous leg ulcers in 1998 and diabetic foot ulcers two years later, while Dermagraft was approved for diabetic foot ulcers in 2001. Both were approved as devices.

Another product marketed for foot and leg ulcers is Kerraboot from Ark Therapeutics Group plc (LSE:AKT, London, U.K.). Kerraboot is a device dressing that absorbs exudate that might otherwise slow healing, while also maintaining a moist wound environment to facilitate healing.

The lone biologic agent on the market in the U.S. and Europe is Regranex becaplermin, a gel formulation of platelet-derived growth factor. PDGF promotes the chemotactic recruitment and proliferation of cells involved in wound repair and enhances the formation of granulation tissue.

Regranex, marketed by Johnson & Johnson (JNJ, New Brunswick, N.J.), received FDA approval in 1997 for diabetic foot ulcers.

Despite the limited number of choices, "early products suffered from poor market penetration," Sheehan noted. "At the time, there were not as many wound healing centers or knowledgeable physicians as there are now. Nurses did not have access to the products because they are prescription, while the skin substitutes needed physicians that had taken the time to learn the application techniques. These products also required reimbursement."

Indeed, sales were underwhelming. While JNJ and Organogenesis do not report sales numbers for their wound healing products, Smith & Nephew plc (LSE:SN;

SNN, London, U.K.) reported annual sales between £3-£7 million (\$6-\$14 million) for Dermagraft during 2002-04, and indeed had stopped selling the product by the time ABH licensed it in 2006.

Growth factor fallout

Aside from Regranex, other growth factors have been looked at without much success, including epidermal growth factor (EGF), fibroblast growth factor (FGF) and transforming growth factor (TGF) beta. These factors play roles in cell division, differentiation, proliferation and organization, and many of these proteins are the targets of potential anti-cancer agents seeking to stop the spread of tumor cells.

There are many theories for the lack of clinical success with growth factors in the wound space. First and foremost is that a chronic wound is a multi-factorial problem involving the interplay among the numerous proteins, tissues and signals.

"Healing a wound is an orchestration of a multitude of growth factors, so the idea that a single growth factor could work by itself was somewhat naïve," said Sheehan.

Among the reasons single growth factors don't work are "a deficiency of growth factors required for normal healing; increased topical concentration of matrix metalloproteinases; impaired fibroblast function with a resultant reduction of collagen synthesis; and abnormal formation of new vessels to adequately nourish the healing wound," according to Nikolaos Papanas, a senior lecturer in internal medicine at Democritus

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— Mount Sinai's Peter Sheehan

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University of Thrace in Greece.

Another problem has been getting the protein where it was needed and keeping it there long enough to have an effect.

“Pharmacologically, a large protein will have trouble penetrating the necrotic, poorly vascularized wound bed in order to get into the reasonably healthy tissue below to allow for the growth of new blood vessels,” said W. Scott Harkonen, president and CEO of CoMentis Inc. (South San Francisco, Calif.), which is working in diabetic ulcers.

Companies also ran into difficulties designing clinical trials. “There was often an unpredictable response rate in the placebo group because patients with non-healing wounds would start getting adequate medical care in the clinical trial

setting,” said Harkonen.

According to Kenneth Thomas, VP of R&D at CardioVascular BioTherapeutics Inc. (CVBT, Las Vegas, Nev.), the heterogeneous nature of chronic wounds also contributed to the failure of some of the early growth factor programs.

“Companies using total wound healing as an endpoint are bound to run into difficulties because there is often too much variability between patients with small and large wounds to get a statistically significant difference among groups in early efficacy trials,” he said.

Faced with such poor odds, a large number of programs in development fell by the wayside (see “Discontinued Agents,” A4).

The market calls

The playing field changed dramatically

with the Vacuum Assisted Closure device from Kinetic Concepts Inc. (KCI, San Antonio, Texas). VAC applies sub-atmospheric pressure to convey negative pressure and maintain sterility to promote healing.

KCI reported \$1.2 billion in revenues from VAC in 2005, the first year the product surpassed the billion-dollar mark. The company posted \$1.4 billion in VAC revenues last year.

“The VAC device became the first wound care product to cross the annual billion dollar sales threshold. That is what really turned everyone’s head, as they saw that there really is market here, and one that hasn’t been captured yet,” Sheehan said.

CoMentis CMO Henry Hsu agreed. “We’ve been working quietly in this area for 18 months or so setting up the Phase

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New agents in the pipeline

While the road has been littered with candidate wound-healing agents, Regranex from Johnson & Johnson and Tracleer from Actelion prove that it is possible to reach the market. More candidate agents are following them into the clinic, at least in part based on improved understanding of the underlying biology of non-healing wounds and increased awareness of the significant market opportunity. (A) Marketed for pulmonary arterial hypertension; (B) Defiante Farmaceutica, a subsidiary of Sigma-Tau, has exclusive rights to TB4 for internal and external wounds in Europe and certain other countries; (C) Epidermolysis bullosa is a group of genetic diseases characterized by skin blistering and lesion formation after minor trauma to the skin; (D) Already in clinic for hypertension

Company	Product	Target	Indication	Status
J&J	Regranex becaplermin	Platelet derived growth factor (PDGF) receptor	Diabetic foot ulcers	Mkt
Actelion	Tracleer bosentan (A)	Endothelin A and B receptors	Digital ulcers	Approved in EU
Biotec Pharmacon	Soluble beta glucan	NA	Diabetic foot ulcers	Ph III
RegeneRx (B)	Thymosin beta 4 (TB4)	NF-kappa B	Corneal wounds; pressure ulcers; venous stasis ulcers; epidermolysis bullosa (C)	Ph II (data 4Q07, corneal); Ph II (others)
Genentech	Topical VEGF	Vascular endothelial growth factor receptor	Diabetic foot ulcers	Ph II (data 1H08)
Agennix	Topical talactoferrin recombinant human lactoferrin (rhLF)	NA	Diabetic foot ulcers; venous and pressure ulcers	Ph II compl (start Ph IIb 2H07, diabetic); Ph I compl (venous and pressure)
King Pharma	MRE0094	Adenosine A2A receptor	Diabetic foot ulcers	Ph II (data YE07/early 08)
CoMentis	ATG002	Nicotinic receptor	Diabetic foot ulcers	Ph IIa (data 1Q08)
Cardium	Excellerate gene therapy	PDGF receptor	Diabetic foot ulcers	Ph I/II compl (start Ph IIb 2H07)
Orthologic	Chrysalin (TP508)	Thrombin receptor	Diabetic foot ulcers	Ph I/II compl (looking to out-license)
CardioVascular BioTherap	CVBT-141B	Fibroblast growth factor (FGF) receptor	Diabetic and venous stasis ulcers	Ph I (Start Ph II 2H07)
U Pennsylvania	Injectable PDGF gene therapy	PDGF receptor	Diabetic foot ulcers	Ph I
CytRx	Iroxanadine	Heat shock transcription factor-1 (HSF-1)	Diabetic foot ulcers	Preclin (start Ph II 1H08) (D)

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Ila study. When we first started, the space was not getting much interest, but in the last six months, we know of six or seven clinical studies that have started in the diabetic foot ulcer space," he said (see "New Agents in the Pipeline," A3).

At the same time, the market opportunity has become more compelling.

"The chronic wound market is growing mainly because of the epidemic of obesity and diabetes," said Sheehan. "We have 21 million patients with diabetes and 54 million with pre-diabetes, so when you factor in that 15% of diabetics can expect to get a non-healing ulcer in their lifetime, it's obviously a big clinical need."

The aging population increases the attractiveness of this market. "Older people are at higher risk of chronic wounds, so the projection is that there will be more and more incidences" of chronic wounds, said David Margolis, associate professor of dermatology at the University of Pennsylvania.

Showing a pharmacoeconomic benefit also looks within reach.

"Anything we can do to prevent or cure foot ulcers is very likely to be cost effective. Even if you spend \$3,000, \$4,000 or even \$10,000 on advanced modalities of treatment, it costs roughly \$60,000 for lower limb amputation, and the hospitalization alone can cost \$16,000-\$20,000 for patients with a diabetic ulcer," said Sheehan. "So if we can find an effective way to treat these non-surgically, then we'll be saving the system a lot of money, which can be an incentive for the biotech industry to focus on this important field."

Healthcare providers have seen the light as well. "In the last

five years, there has been a proliferation of wound centers because hospitals realize that the patients they attract are ones with chronic wounds that also often have something like Type II diabetes, meaning they are 'high utilizers.' These wound centers also offer things like hyperbaric oxygen treatments, which generate ancillary revenues for the hospitals," said Sheehan.

Growth factors revisited

Some companies remain convinced that single growth factors have a role to play in treating chronic wounds. One of these is Genentech Inc. (DNA, South San Francisco, Calif.), which has a topical VEGF agent in Phase II testing for diabetic foot ulcers.

"While the wound healing process is complex and requires the orchestration of numerous factors, we believe VEGF may be more important than other growth factors that have been studied in the past based upon the common observation that establishment of a healthy blood supply to the wound is a critical element for timely wound closure," said spokesperson Dawn Kalmar.

CVBT also is developing a topical growth factor, in this case FGF-1, which is in Phase I testing for diabetic ulcers. Thomas, who helped discover and characterize FGF-1 and later develop it as a therapeutic at Merck & Co. Inc. (MRK, Whitehouse Station, N.J.), said the protein potentially stimulates mitogenesis and chemotaxis in fibroblasts, keratinocytes and microvascular endothelial cells.

The last of these is particularly important to FGF-1's angiogenic activity, he added.

Thomas said both FGF-1 and FGF-2 are more potent than PDGF and VEGF "in a healing-compromised animal model like

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Discontinued agents

Selected setbacks for chronic wound agents. Many of the failed compounds were among the first wave of growth factors that entered the clinic in the mid- to late 1990s. (A) In 2000, Genzyme Tissue Repair merged with Genzyme Surgical Products and Biomatrix to create Genzyme Biosurgery, which was later folded back into Genzyme (GENZ) in 2003

Company	Product	Reason for discontinuation
Genzyme	Vianain ananain debriding enzyme	In 1995, the company's Genzyme Tissue Repair division completed Phase II testing of Vianain for burn wounds and Phase I testing for chronic skin ulcers (venous, diabetic and pressure). The compound was later discontinued. (A)
Genzyme/Celtrix (acquired by Insmed in 2000)	Recombinant transforming growth factor (TGF) beta 2	Genzyme Tissue Repair dropped TGF beta 2 for diabetic foot ulcers in 1999 to streamline its operations; the product completed Ph II testing in 1998 (A)
Human Genome Sciences	Repifermin keratinocyte growth factor (KGF) receptor agonist	Failed Phase II trial for chronic venous ulcers in September 2003
Inspire/Allergan	Diquafosol tetrasodium P2Y(2) receptor agonist	Discontinued for corneal wounds in August 2005 after enrollment was halted in a Phase II trial in New Orleans following Hurricane Katrina. Based on a review of the limited data available, ISPH said it did not plan to pursue this indication. The company is developing the product for dry eye, for which it received a second FDA approvable letter at the end of 2005.
ProCyte (acquired by PhotoMedex in 2005)	Iamin topical peptide-copper compound	Failed Phase III trial in diabetic foot ulcers in 1994. The gel received 510(k) clearance by FDA as a device in 1996 as a hydrating wound dressing.
Telios (acquired by Integra in 1995)	Argidene gel consisting of the peptide sequence arginine, glycine, aspartic acid complexed with hyaluronic acid	Failed in pivotal trials in both diabetic foot ulcers and venous stasis ulcers, 1993-95

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a diabetic mouse, where angiogenesis is the most important rate-limiting step.”

However, while FGF-1 stimulates all seven FGF receptors, FGF-2 stimulates only five of the seven. The two remaining receptors regulate epidermal keratinocytes, which is why CVBT believes its FGF-1 agent will prove more effective than agents addressing FGF-2.

The company's topical FGF-1 is in the process of moving from a single-dose to multi-dose Phase I trial to treat dermal diabetic and venous ulcers. Results should be available sometime next year, Thomas said.

Kaken Pharmaceutical Co. Ltd. (Tokyo, Japan) has reached the market with an FGF-2 product. Fiblast trafermin, licensed from Scios Inc., now a subsidiary of JNJ, was approved for chronic dermal ulcers in Japan in 2001.

Tomohiro Takaya, a manager at Kaken, said the company is looking for partners in the U.S. and Europe to take over responsibility for developing and marketing Fiblast in those territories.

According to Sheehan, growth factors are especially challenged in the wound setting.

“Growth factors are all peptides, and the wound site is a very inhospitable environment that is filled with proteases, matrix metalloproteinases, and inflammatory cells that digest and denature peptides quite quickly,” he said.

As a result, use of even a clinically relevant agent like Regranex involves sticking to a demanding treatment schedule that severely limits patient compliance. Christopher Reinhard, chairman, president and CEO of Cadium Therapeutics Inc. (CDTP, San Diego, Calif.), noted that Regranex must be applied to a wound and then allowed to sit for 12 hours, washed off and allowed to sit for 12 hours, then re-applied for another 12 hours. “This is challenging for patients,” he said.

CDTP hopes to avoid the compliance issue by using gene therapy. The company's solution is Excellerate, a DNA-based topical collagen gel formulated with an adenoviral vector encoding human PDGF BB. In a Phase I/II trial, over 80% of diabetic patients receiving a single dose or four once-weekly doses of Excellerate had complete wound closure after 14 weeks.

Reinhard expects the product, which will start Phase IIb testing for diabetic foot ulcers this half, will require only one or two administrations.

The company obtained the product last year from Tissue Repair Co., which is now a subsidiary of CDTP (see *BioCentury*, Aug. 21, 2006).

At the University of Pennsylvania, Margolis is working with a group developing a similar gene therapy involving PDGF, but the academics are delivering the agent subcutaneously. The group is conducting an NIH-sponsored Phase I trial of a single injection of an AAV vector encoding PDGF in 15 patients who are then followed for four weeks.

“Historically, the growth factors have always been applied topically, but the results have been uniformly underwhelming,” he said. “Our experience with the AAV vector suggests the problem was the delivery, meaning that previous agents were not

successfully penetrating the wound site.”

Margolis believes wound healing may be the ideal setting for gene therapy. “We're not looking at an illness caused by a deficiency of a certain protein where we'd need to try to change the body's ability to produce a protein over a long period of time,” he said. “We're just inducing the body to make more of this protein for a couple of weeks.”

Twelve of a planned 15 patients have been enrolled in the Phase I trial, which Margolis expects to finish in the next year or so, as the school has been cautious about gene therapy trials following the death of a patient in an unrelated gene therapy trial in 1999 (see *BioCentury*, Oct. 4, 1999). Next up would be a Phase Ib or Phase II trial that would be conducted by the NIH or possibly an industry partner.

In contrast to the single factor approach, Agennix Inc. (Houston, Texas) is banking on being able to stimulate multiple growth factors.

“Wound healing is a complex, multi-step biological process, which requires drug action on multiple factors,” said VP of R&D Karel Petrak. “Several cytokines and chemokines are essential for an effective acute inflammatory phase, an early step of the wound repair process. This is followed by the activity of additional growth factors and dermal cells that contribute to effective wound closure. Several of these steps can be impaired in patients with chronic wounds, especially in patients with diabetes.”

Petrak said Agennix's talactoferrin alfa, a recombinant human lactoferrin (rhLF) immunomodulatory protein, “acts at the wound surface, binding to receptors on dermal and immune cells and inducing the release of key cytokines and chemokines essential for tissue repair.” As a result, the product “enhances the early inflammatory stage that is required for effective wound healing,” he said.

Agennix reported that compared with placebo, twice as many patients with diabetic neuropathic ulcers given topical talactoferrin had a 75% reduction in ulcer size, which met the primary endpoint in a 12-week Phase II trial (see *BioCentury*, June 20, 2005).

Next half, the company plans to start a Phase IIb trial in diabetic foot ulcers and a Phase II trial in venous and pressure ulcers.

Managing inflammation

Sheehan argues for an even more interdisciplinary approach. Rather than focusing solely on growth factors, “another idea for addressing these non-healing wounds would be small molecules, which are stable and can act as ligands to signal the desired effect,” he said.

King Pharmaceuticals Inc. (KG, Bristol, Tenn.) is doing just that by developing MRE0094, a topical small molecule agonist of the adenosine A2A receptor. It is in Phase II testing for diabetic neuropathic foot ulcers.

Bruce Cronstein, who owns the patent for use of adenosine A2A receptor agonists for chronic wounds that is licensed to KG, told *BioCentury* MRE0094 has the potential to promote wound healing in a number of ways. Stimulating the adenosine

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— U of Texas' Lisa Gould

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A2A receptor restricts inflammation by down-regulating matrix metalloproteinases (MMPs) and pro-inflammatory cytokines, helps to increase blood vessel formation by boosting VEGF production and endothelial cell proliferation, and boosts collagen production.

Indeed, while the inflammatory response is required to initiate healing, it is also a culprit in long-lived wounds.

"Most chronic ulcers are characterized by the presence of increased inflammatory cells, and at a certain point they contribute to a vicious cycle of increasing inflammation and local tissue destruction because of their production of inflammatory mediators that, in small amounts, would be beneficial," said Cronstein, who is a professor at the New York University School of Medicine.

RegeneRx Biopharmaceuticals Inc. (RGN, Bethesda, Md.) believes its thymosin beta 4 (TB4), a synthetic version of a naturally occurring peptide present in most human cells, may also affect multiple pieces of the puzzle.

Spokesperson J.J. Finklestein said pre-clinical data show TB4 helps regulate the binding of actin and the production of laminin-5, proteins involved in cell structure and adhesion, respectively. In addition, a study by NIH suggests TB4 helps regulate expression of MMPs, including MMP-2 and MMP-9, which play an important role in the healing process.

RGN expects data toward year end from an ongoing Phase II trial in chronic pressure ulcers. The company began a Phase II trial to treat corneal wounds last quarter.

Vasculature is key

Taking a cue from the intended role of many of the growth factors, companies are looking at a number of different strategies for improving missing or damaged vasculature as way of facilitating healing.

The clinical experience of Tracleer bosentan from Actelion Ltd. (SWX:ATLN, Allschwil, Switzerland) is one example of an agent with vasodilatory effects that works in a wound healing setting. Last month, the European Commission approved the oral dual endothelin A and B receptor antagonist to reduce the number of new digital ulcers in patients with systemic sclerosis (see *BioCentury*, June 18).

ATLN already markets Tracleer to treat pulmonary arterial hypertension (PAH).

CoMentis, formerly known as Athenagen, is developing a small molecule nicotinic acetylcholine receptor (nAChR) agonist that stimulates angiogenesis in the periphery. According to Harkonen, the blood supply gradient in a wound ranges from very good in deep tissue, but is basically non-viable towards the surface, meaning it won't heal because there is simply not enough blood.

"A very small molecule like nicotine can penetrate the necrotic, poorly vascularized tissue in order to stimulate blood vessel growth," he said.

The company's ATG002 topical gel is in a 48-patient Phase IIa trial for diabetic foot ulcers, in which the company is evaluating both complete wound closure and rate of wound

closure. Data are expected by 1Q08.

CytRx Corp. (CYTR, Los Angeles, Calif.) is approaching the circulatory deficit associated from a different angle with its irovanadine.

"Drugs to date are more like Band-Aids that address the symptoms but not the underlying causes" of diabetic wounds, said CSO Jack Barber. "I believe that repairing proteins that have become misfolded as a result of the diabetic condition could help restore normal vascular function and repair wounds."

While misfolded proteins are often associated with progressive neurological disorders like Alzheimer's disease (AD) and Parkinson's disease (PD), Barber said protein aggregates are also found in the pancreas of Type II diabetics.

"Stressful conditions such as ischemia or hyperglycemia can result in misfolded proteins, but the body's natural response to

this is to produce chaperone molecules like heat shock proteins that unfold proteins and then allow them to refold properly. Irovanadine works by stabilizing the phosphorylation of heat shock transcription factor I, which amplifies the expression of the chaperones," he added.

In a Phase II trial in patients with high blood pressure, CYTR learned that irovanadine improves vascular endothelial cell function, which in theory is a major reason for the lack of proper blood

flow to a wound site. The company plans to start a Phase II trial to treat foot ulcers in diabetic patients in 1H08.

CYTR acquired irovanadine (BRX-235) in 2004 from Biorex Research and Development Co. RT (Veszprém-Szabadságpuszta, Hungary) (see *BioCentury*, Oct. 11, 2004).

Sheehan believes another strategy will be to turn to agents in development for circulatory problems, particularly those in the lower extremities that are a major cause of non-healing wounds.

"When you have a wound due to poor circulation or something like critical limb ischemia, healing it often requires some sort of surgical revascularization, which has shown pretty good long term results," he said. "I think there are opportunities for something like a gene therapy either to help a patient get through an episode or forestall the need for surgery. Plus there are patients with no surgical options for anatomical or high-risk reasons who could benefit."

AnGes MG Inc. (Tokyo:4563, Osaka, Japan) is taking this route with a gene therapy utilizing hepatocyte growth factor (HGF), also known as scatter factor, a protein that promotes the regeneration of blood vessels. Last month, the company reported that its AMG0001 injectable HGF met the primary endpoint in a Japanese Phase III trial to treat critical limb ischemia (CLI). Significantly more patients receiving AMG0001 showed improved pain at rest (according to visual analog scale) or ischemic ulcer size at 12 weeks versus those receiving placebo ($p=0.014$).

Daiichi Sankyo Co. Ltd. (Tokyo:4568; Osaka:4568, Tokyo, Japan) has sales and marketing rights to AMG0001, which uses DNA delivery technology from Vical Inc. (VICL, San Diego, Calif.).

sanofi-aventis Group (Euronext:SAN; SNY, Paris, France) also has moved into Phase III testing with NVIFGF (XRP0038), a DNA plasmid encoding FGF-1 to treat CLI. As with AMG0001, the product also uses VICL's DNA delivery technology.

While the agent failed to significantly improve the primary endpoint of ulcer healing in the Phase IIb TALISMAN 201 trial,

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— W. Scott Harkonen of CoMentis

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the pharma company said it would move ahead with a Phase III trial this year that will use a combined primary endpoint of major amputation or death (see *BioCentury*, March 20, 2006).

Other agents in the same vein include Tissue Repair Cells made from bone marrow, which Aastrom Bioscience Inc. (ASTM, Ann Arbor, Mich.) has in Phase IIb testing to treat CLI in PAD patients; and EW-A-401, a polymer formulation of a plasmid DNA encoding a ZPF transcription factor from Sangamo BioSciences Inc. (SGMO, Richmond, Calif.). The latter has completed Phase I trials for CLI and intermittent claudication.

"There is a lot of very high tech stuff going on in this field, which is being driven by procedural advances, but if a clinician can improve circulation, they will greatly improve the chances of overcoming problems with non-healing wounds," said Sheehan.

New ideas

Impaired angiogenesis and vasculogenesis also have been established as contributing to deficient wound healing, and several recent publications have described new targets in this area.

According to Omaid Velazquez, assistant professor of vascular surgery at the University of Pennsylvania School of Medicine, studies have shown that bone marrow-derived endothelial progenitor cells (EPCs) play a key role in the formation of new blood vessels. Hyperoxia has been shown to boost EPC mobilization but without a similar increase in vasculogenesis. This disconnect has never been explained.

In May, Velazquez and her group published in the *Journal of Clinical Investigation* that the missing link could be SDF-1a, which mediates EPC recruitment and is largely lacking at wound sites. In a diabetic murine model exposed to hyperbaric oxygen therapy, "EPCs were mobilized to the circulation but did not home in on wounds because of the deficiency in SDF-1a. The combination of hyperoxia and SDF-1a then accomplished both an increase in the EPC circulating pool and homing the EPC to the wounds," she told *BioCentury*.

Velazquez said the next step would be "to determine if SDF-1a deficiency is a predictor of poor wound healing in human patients with diabetes-associated wounds."

The university has filed a provisional patent on the work, but so far there has been no contact with industry, she added.

Another group interested in the therapeutic potential of EPCs, from the Institut des Vaisseaux et du Sang in Paris, also reported in the June *JCI* that activating a pathway involving EphB4, an Eph receptor in the tyrosine kinase protein family, led to the increased adhesion of EPCs at the surface of ischemic endothelium. The researchers suggested that EphB4 activation could be a useful method for improving the efficiency of cell-based pro-angiogenic therapies.

Gérard Tobelem told *BioCentury* his group plans to expand the preclinical work to further establish safety while also determining how durable the angiogenic effects are.

"This process is protected by patents, and we started to discuss with potential industrial partners, which are biotech companies involved in cell therapy, but we are still open to new discussion

since we did not yet sign any agreement," said Tobelem, who serves as director of the institute at the Lariboisiere Hospital.

Stem cells also are gaining attention. In May, researchers from the Roger Williams Medical Center and Boston University School of Medicine reported in *Tissue Engineering* that a fibrin polymer spray infused with autologous mesenchymal stem cells (MSCs) stimulated closure of full thickness wounds in diabetic mice.

The therapy was also safely administered to patients with chronic wounds, who also generated new elastic fibers, with a strong correlation between number of MSCs applied and decrease in wound size.

Vincent Falanga, professor of dermatology and biochemistry at the medical school and a study author, said the group plans to conduct an expanded study with more subjects using the same MSCs, but has not yet started discussions with potential partners.

It is doubtful that the fibrin delivery method is patentable, he noted, but the researchers are evaluating another method that they may seek to patent.

Calretex LLC (New York, N.Y.), which was spun out of the New York University Medical School in 2003, believes that a protein called calreticulin may prove to be a key ingredient for promoting proper wound healing.

Leslie Gold, an assistant professor of medicine and pathology at NYU and an author of the patent covering calreticulin's utility for wound healing, said preclinical results suggest the protein "targets both the epithelium and dermal components of skin as shown by its ability to accelerate re-epithelialization of wounds as well as induce dermal matrix formation by remodeling and filling in the wound."

Gold added that calreticulin "induces proliferation of keratinocytes and fibroblasts and stimulates migration of keratinocytes, fibroblasts, macrophages and monocytes. These are the cells that migrate into the wound required for healing and remodeling. Calreticulin also stimulates specific components of the dermal matrix, such as fibronectin."

The company is preparing for a pre-IND meeting scheduled with FDA in mid-2007 and hopes to start a Phase I/II trial to treat chronic diabetic foot ulcers in 2008.

Better practices

In the meantime, companies are working to improve on trial designs, so that the next-generation approaches are able to demonstrate an improved result.

"One solution is to bring potential patients in for a screening period of two weeks where everybody gets good wound care," said Harkonen of CoMentis. "If they start achieving something like 30% wound closure, then they are not eligible to be enrolled. If, on the other hand, they have not started healing at that point, then you enter them into the trial."

CVBT's Thomas believes the best way to deal with the heterogeneity problem is to use the endpoint of healing distance rather than complete healing.

"This appears to be the best way to analyze wound healing to account for different sized wounds," he said, "because you can use the perimeter, distance and surface area of a wound to calculate as a function of time how fast a wound is healing in from the edge, independent of the size of the wound."

'Wound healing is a complex, multi-step biological process, which requires drug action on multiple factors.'

— Karel Petrak of Agennix