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New therapeutics for the prevention and reduction of scarring

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Published literature shows that both physicians and patients are highly concerned about scarring and value even small improvements in scar appearance. Both severe and relatively minor scars can have a significant psychological impact on patients, irrespective of whether or not they are hidden by clothing.There is no universal standard of care for scarring and, currently, no marketed pharmaceuticals for the prophylactic reduction of scarring. Novel approaches are under development, with the furthest progressed being avotermin (Juvista; transforming growth factor beta 3). The scar-improvement efficacy of this agent, administered at the time of surgery, has been demonstrated in robust, well-controlled, randomized human studies. Avotermin and other agents in development represent a new class of prophylactic medicines promoting the regeneration of normal skin and improving scar appearance.

Few humans reach adulthood without experiencing a wound to the skin that results in a scar. Scars range from fine lines (e.g. following plastic surgery) to raised, hard, red, pruritic and painful hypertrophic or keloid scars, which are severely disfiguring and cause significant morbidity. In addition to physical complications, the appearance of scars can be a major concern for both physicians and their patients. Published literature shows that wide demographic groups, across gender, age, ethnicity and geographical region, have similar concerns about scarring and that patients, in particular, value even small improvements in scarring [1–8].

It is well established that severe and disfiguring scarring can be associated with significant psychological stress and impairment of quality of life [9–16]. Studies, however, also show that scarring, which may be considered minor, can also have significant psychological impact on patients, particularly when located on a visible body site [17,18]. Changes in texture, skin discoloration, depressed or raised scarring and loss of symmetry may be of equal concern to patients with relatively minor wounds as to those with severe scarring and disfigurement [15,19,20]. Patients are not only concerned about the scars on visible body parts [10,21]. For example, studies have revealed high levels of dissatisfaction among patients with scars developing at graft donor sites used for breast reconstruction [22], following surgery for congenital heart disease [3] and following elective procedures such as abdominoplasty [23,24].

Scar prevention and reduction is a therapeutic area of unmet medical need and opportunity

Existing scar treatments are used predominantly to treat excessive scarring resulting from extreme or chronic wounds, and the only published clinical guidelines for scar management focus predomininantly on severe scars, particularly hypertrophic scarring and keloids [11,25]. There is, however, increasing focus on optimizing scarring following elective surgery and the increasing popularity of minimally invasive and cosmetic surgery underscores this trend. Scarring outcomes following surgery can be difficult to predict. One aesthetic surgeon has provided the following insight: ''My goal is always to restore or improve appearance. How close I come to achieving that goal depends on my surgical skill, their healing ability, and a little bit of luck. I mention [to the patient] that sometimes a secondary procedure may be required for the best result'' [26]. Many patients seek surgery for scar revision, but market research indicates that surgeons turn away large numbers of patients, as they believe that an improved result could not be achieved with current techniques and therapies (National Center for Health Statistics Survey, Centers for Disease Control and Prevention, USA: http://www.cdc.gov/nchs/data/hdasd/13_139t9.pdf).

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BOX 1

Summary of non-surgical therapies currently used for the management of scarring

Therapy	Modality
Vitamin E	Topical preparation (anecdotal)
Onion extract (Mederma)	Topical preparation [64]
Corticosteroids	Pharmaceutical [65]
Compression garments	Wound dressing [66]
Adhesive microporous paper tape	Wound dressing [67,68]
Hydrogel sheeting	Wound dressing [69]
Silicone sheeting	Wound dressing [34,70,71]
Nonablative lasers	Laser [72,73]
Ablative lasers	Laser (removes scar surface or whole scar) [74–76]
Chemical peel	Surgical (removes scar surface) [77]
Alloderm	Skin substitute (acellular human allograft) [78]
Integra dermal regeneration template	Skin substitute (artificially manufactured matrix) [79]
Epicel	Skin substitute (autograft keratinocytes) [80,81]

Market research indicates that, in the US alone, approximately 45 million patients per annum undergo procedures that would benefit from a scar-reduction therapy, which is comparable to other major therapeutic/disease indications ([27]; source: independent research conducted by the Mattson Jack Group on behalf of Renovo, 2004). The high incidence of scarring, along with patients, concerns about scarring and the frequency of scar revision required following injury or procedures, clearly identifies scarring as an area of high and, as yet, not suitably met medical need.

Current therapies for treatment/reduction of scarring versus a prophylactic and regenerative approach

A wide range of treatment paradigms has been evaluated for the management of scarring, with most used to treat scars that have already formed (Box 1). No single therapy has been universally adopted as the standard of care for clinical practice [25,28–30]. A new concept for scar management that we are pioneering is the prophylactic reduction of scarring by pharmaceutical agents that are given at the time of surgery to reduce subsequent scar formation. Currently, there are no marketed pharmaceuticals for the prophylactic improvement of scar appearance. The range of treatments used in clinical practice tends to have unclear mechanisms of action and have shown unpredictable, limited and variable effectiveness [28,30–35]. These typically require repeated and long-term treatment, can be associated with unwanted side effects and can result in scar recurrence. A major limitation of this therapeutic area is that treatments have not generally been evaluated in prospective or robust randomized clinical trials.

Discovery and development of prophylactic scar-reduction therapeutics

To facilitate the discovery and development of effective prophylactic treatments, there was a clear requirement for the understanding of the processes involved in scarring at the molecular, cellular, tissue and clinical levels. Once identified, the clinical efficacy and safety of novel therapeutics needs to be demonstrated in prospective, well-controlled, double-blind clinical studies with defined, robust and relevant efficacy endpoints.

The multiple, overlapping molecular and cellular components of healing and scarring are complex and ultimately result in the restoration of tissue following injury. This normal healing response in the skin, and alterations to it, can result in significant clinical morbidity, for example in chronic wounds (which fail to heal adequately) or in excessive healing and scarring in the case of hypertrophic scars and keloids (Figure 1). Studies have shown that understanding the mechanisms of the scarring response, along with its appropriate and subtle modulation, can lead to the regeneration of tissue that is more similar to normal skin and has led the way to identifying feasible new therapeutic options [36].

In terms of the discovery of targets or pathways for the modulation of scarring, further understanding of the exact mechanisms underlying this process in relevant preclinical and clinical models is required. Using a range of preclinical foetal, transgenic and adult models (in species including mice, rats, rabbit, sheep and pigs), the mechanisms underlying wound healing and scarring have been evaluated and facilitated the development of rationally based scar-improvement agents for clinical evaluation ([36–38]; Table 1). While these models share numerous features of wound healing and scarring with humans, to date no published studies have extensively compared the molecular mechanisms and efficacy of scar reduction therapies between preclinical models and humans. To this end, a longitudinal study was conducted that compared gene-expression profiles (using the Affymetrix Gene Chip platform) during wound healing and scarring following full-thickness cutaneous wounds made in a rat model and humans (Renovo, data on file). Samples were collected from the time of wounding to 84 days post-wounding in the rat (>250 samples; 14 timepoints; ~16 000 genes per sample per timepoint) and to one year post-wounding in humans (>800 samples; 18 timepoints; 12 500–30 000 genes per sample per timepoint). The gene-expression data generated confirmed that there is significant molecular comparability between the healing and scarring processes in both species. Further evidence for similarities is provided by the preclinical and clinical efficacy of scar-improvement therapeutics with different mechanisms of action, which is discussed below.

Clinical evaluation of scar-improvement therapies

One approach for the development of therapies has focused on development of agents for the prophylactic reduction of scarring. This approach involves agents that are administered locally at the time of surgery, or injury, that lead to long-term improvements in scarring. In this way, the mechanism of action and administration of candidate products align with current clinical practices. This is a novel pharmaceutical approach to scar improvement and there are challenges associated with designing clinical trials in this pioneering therapeutic area, which include evaluating the effectiveness of a prophylactic drug. There is no established baseline against which to determine improvements in scarring (since baseline would otherwise be normal skin before surgery or injury) and it is well established clinically that patients vary markedly in their propensity for scarring [6,25]. Clinical experience has shown that the most robust clinical trial design for randomized scar-improvement studies is a within-subject control. Such a design ensures that

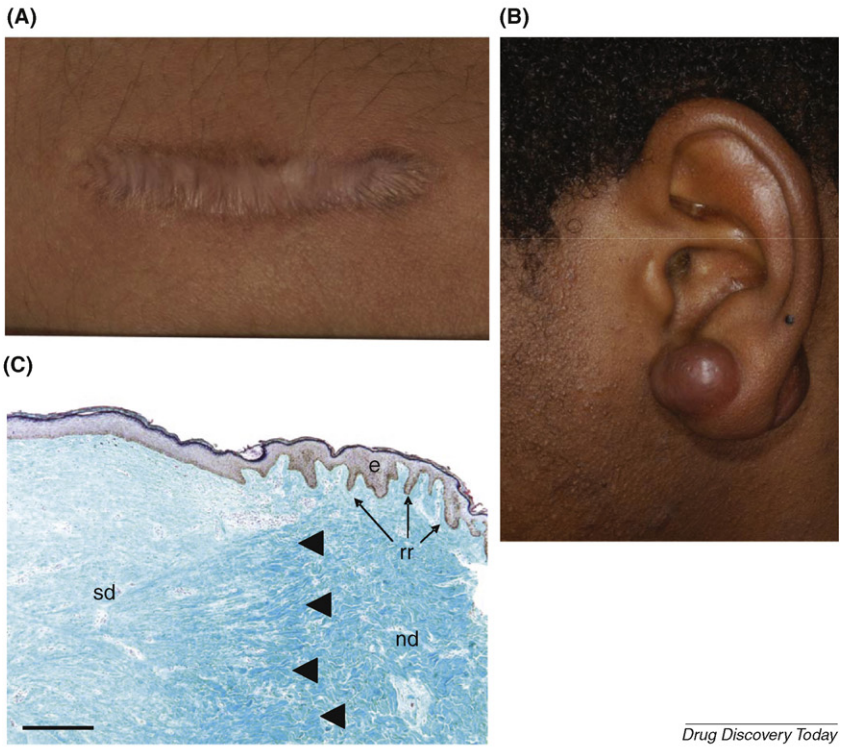

FIGURE 1

Macroscopic and microscopic appearance of disfiguring scars.
Macroscopic photographs of a hypertrophic **(A)** and a keloid **(B)** scar. A histological tissue section through a hypertrophic scar (C) demonstrates the 'basket weave' appearance of the collagen in normal skin (dermis; nd) and the structure of the epidermis (e), which includes rete ridges (rr). This contrasts with the altered architecture of collagen in the scarred dermis (sd), which shows parallel bundles of collagen with reduced fibril diameter, and a lack of rete ridges in the reformed epidermis. Arrowheads indicate the scarred dermis and normal dermis interface; scale bar = 1000 μm.

treatment is the only major variable with the potential to significantly affect scarring at control- and active-drug-treated sites and minimizes confounding effects from a range of genetic, environmental, patient (e.g. skin type) and surgeon-specific variables that may impact on the final scar appearance.

Emerging scar-reduction therapeutics

Understanding of the biological and cellular mechanisms of scarring has led to new therapeutic approaches for scar reduction in the skin, and at other body sites, that are undergoing commercial development. A number of companies are investigating a range of devices as scar-improvement therapies (e.g. silicon sheets, patient-derived fibroblasts). Others are focusing on the development of molecular approaches for the development of new pharmaceuticals (Table 1). Some of the pharmaceutical candidates are at the stage of evaluation in preclinical animal models, while others are currently under evaluation in different phases of human clinical trials. As indicated in Table 1, the pharmaceutical approaches for prophylactic scar improvement that have advanced most in clinical development during the past one to two years are avotermin (Juvista; recombinant human transforming growth factor beta 3; rhTGFβ3) and ilodecakin (recombinant human interleukin- 10; IL10). Both agents have progressed through evaluation in prospective, randomized clinical trials in human volunteers, which incorporate within-subject controls and relevant efficacy endpoints. As well as providing evidence of the safety of the agents in humans, these trials have provided for controlled and robust proof-of-concept testing of scar-improvement efficacy.

Avotermin (recombinant human transforming growth factor beta 3; rhTGFβ3)

Research into the mechanisms of scar-free healing in the embryo identified the members of the TGFβ family of growth factors as key proteins involved in scar formation [38–43]. Avotermin is the recombinant human form of TGFβ3, which is present at high levels in developing embryonic skin and in embryonic wounds that heal with no scar. By contrast, TGFβ3 is present at low levels in adult wounds that scar. Subsequently, extensive preclinical studies have evaluated the mechanism of action and efficacy of avotermin. Evidence to support the clinical development of avotermin was obtained from a variety of animal models, with results indicating that avotermin is a new class of regenerative medicine that promotes regeneration of normal skin and improves scar appearance. On the basis of evidence from these preclinical studies, avotermin is postulated to promote the regeneration of normal skin and improve scar appearance by the following mechanisms: (1) influencing the organization of the newly deposited extracellular matrix in the wounded dermis such that it more closely resembles normal, uninjured skin; (2) reducing the deposition of excessive extracellular matrix (e.g. fibronectin and collagen) in the

TABLE 1

Pharmaceutical approaches under evaluation for scar improvement.

Company	Molecule/mechanism of action or approach	Phase of development	Therapeutic area and supporting data
CoDa Therapeutics (New Zealand)	*Nexagon*: an anti-connexin oligonucleotide that has been shown to accelerate wound healing	Preclinical	*In vivo* results indicate a decrease in inflammation and neutrophil levels and decreased granulation tissue leading to a smaller, less contorted scar [82]; nexagon accelerated re-epithelialization in an *in vivo* ocular study (Patent WO05053600A2); clinical studies planned in wound healing in the skin and eye (http://www.codanz.com)
Eyegene (S Korea)	*EGS-001*: bone morphogenetic protein-7 polypeptide that inhibits differentiation of fibroblasts and reduces fibronectin expression	Preclinical	*In vitro* data indicate induction of apoptosis in lymphocytes, inhibition of fibroblast differentiation and growth of myofibroblasts and reduced fibronectin expression; evaluated for the treatment of ocular scarring following surgery [83]
Excaliard (USA)	Stabilized 20-mer oligo-deoxynucleotide, anti-sense to connective tissue growth factor (CTGF)	Preclinical	Preclinical data from rabbit models of cutaneous and ocular (glaucoma filtration surgery) scarring demonstrated reduced scar elevation (skin) and reduced scarring (eye); information available at http://excaliard.com [84]
FibroGen (USA)	*TGFβ antagonists*: a series of small molecules selectively affecting the downstream pro-fibrotic events of TGFβ	Preclinical	In development for the treatment of fibrosis and cancer, with clinical candidate planned (http://www.fibrogen.com/rd/tgf-beta/)
First String (USA)	Polypeptide based on the carboxy-terminal amino acid sequence of an α-connexin	Preclinical	Evaluated for wound healing, reduced scarring and tissue regeneration, targeting patients with acute and chronic wounds (www.firststringresearch.com); treatment anticipated to be topical with the intention to dose at wounding and 24 h later for acute wounds and 'frequently until healed' for chronic wounds; preclinical efficacy has been demonstrated in mouse (adult and neonates) and pig models, with no signs of adverse reactions
Neuraxo (Denmark)	*Cordaneurin*: inhibits collagen scar formation, allowing injured nerves to reattach more effectively	Preclinical	Cordaneurin prevents collagen scar formation enabling injured nerves to extensively regenerate over long distances in their natural nerve tract [85]; clinical studies are planned
Pfizer (UK)	*UK-369930*, *UK-389228*, *UK-421045*, *UK-424134*: inhibitors of procollagen-C-proteinase (PCP) and subsequent collagen deposition	Preclinical	PCP inhibitors showed good efficacy *in vitro* in models of fibroplasia and trans-epidermal reflux [86]; no development reported since September 2005
Pharmaxon (France)	*PR-21S*: cyclic 12-amino acid mimotope of polysialylated form of neural cell adhesion molecule (NCAM); inhibits glial scarring and activity of axon growth inhibitor; promotes cell migration, axonal path finding and targeting	Preclinical	Selectively inhibits glial scar development while stimulating nerve regeneration *in vivo*; clinical studies planned in spinal-cord injury (http://www.pharmaxon.com)
Phylogica (Australia)	*PYC-35B*: anti-inflammatory	Preclinical	*In vivo* data indicate acceleration of healing of burns and reduced scarring; clinical studies planned in partial thickness burns (http://phylogica.com/)
FibroGen (USA)	*FG-3019*: IgG1 antibody that binds specifically to domain 2 of connective tissue growth factor and blocks both angiotensin II and advanced glycation end product-induced fibronectin production by vascular smooth muscle cells	Phase I	FG-3019 has been shown to reduce or inhibit fibrosis in lung, liver and kidney *in vivo*; it is in development for treatment of idiopathic pulmonary fibrosis (phase I complete), focal segmental glomerulosclerosis (phase I planned), and other diseases (http://www.fibrogen.com/programs/fg-3019/)
Orthologic (USA)	*AZX-100*: 24 amino acid peptide analogue of heat shock protein 20, an intracellular actin-relaxing molecule	Phase I	Phase I study in healthy adult males completed with acceptable safety profile (http://www.orthologic.com/research-development/AZX100.php); further phase I study in dermal/hypertrophic scarring planned
Ambrilia Biopharma (Canada)	*Fibrostat*: putrescine; inhibitor of tissue transglutaminase (collagen cross-linking)	Phase II (Discontinued)	Phase II b study evaluated as treatment for hypertrophic scarring: treatment showed no greater efficacy than placebo (http://www.ambrilia.com/en/investors/news.php)

TABLE 1 (*Continued*)

Company	Molecule/mechanism of action or approach	Phase of development	Therapeutic area and supporting data
ItherX (USA)	***ChelASE/VIT-100***: vasoprotectant, adenovirus-based gene therapy	Phase II (Discontinued)	Proposed for the treatment of keloids, proliferative vitreoretinopathy and other diseases; phase II clinical data for proliferative vitreoretinopathy reported to be negative (source: www.thomson-pharma.com)
Laboratoire Besins (Belgium)	*Afimoxifene*: tamogel; estrogen receptor antagonist	Phase II	Afimoxifene is under investigation for keloid scarring and other diseases; phase II trials for treatment of keloid scarring initiated July 2004 but not yet reported (source: www.thomson-pharma.com)
Renovo (UK)	*Juvidex*: mannose-6-phosphate; reduces the activation and pro-fibrotic effects of TGFβ1	Phase II	Trend towards efficacy in randomized, double blind, placebo-controlled phase II study in the skin (http://www.renovo.com)
Renovo (UK)	*Ilodecakin*(Prevascar): recombinant human interleukin-10 (IL10); immunomodulation	Phase II	Significant scar reduction when administered to full-thickness skin incisions in a randomized, double-blind, placebo controlled phase II study (see also text; http://www.renovo.com)
Renovo (UK)	*Avotermin* (Juvista): recombinant human TGFβ3; alters healing environment to more closely resemble that of fetal scar-free healing	Phase II	Significant scar reduction in seven randomized, double-blind, placebo controlled studies in the skin (see also text; http://www.renovo.com)
Biospecifics and Auxilium (USA)	*AA-4500*: stimulates collagenase activity	Phase III	Results from a randomized, double-blind, placebo controlled phase III study demonstrated efficacy when administered locally to treat Dupuytren's contracture (source: http://www.clinicaltrials.gov)
Kissei (Japan)	*Tranilast*: histamine H1 receptor antagonist, vasoprotectant, analgesic, anti-inflammatory	Marketed	Inhibits synthesis of type I and III collagen *in vitro*; when administered with TGFβ1 found to inhibit the stimulatory effect of TGFβ1 on collagen synthesis; tranilast also inhibited collagen synthesis in scleroderma fibroblasts and keloid fibroblasts [87]; tranilast *in vivo* reduces collagen content of granulation tissue in a dose-dependent manner [88] Marketed for treatment of bronchial asthma in 1992 in Japan and Korea; indication for hypertrophic scarring approved in 1993 for these countries (http://www.nuontherapeutics.com/company/pr_2007-07-23.html)

wound; (3) normalizing the phenotypic appearance of the dermis; (4) modulating the inflammatory response by decreasing the number and persistence of inflammatory cells at the wound site; (5) accelerating the scar-maturation phase [36,44,45].

Preclinical studies demonstrated a significant reduction in scarring when administered intradermally at the time of surgery at concentrations of 50 and 100 ng/100 μL/linear cm. Compared with placebo-treated wounds, administration of avotermin was associated with the deposition of extracellular matrix (collagen) that had a markedly improved architecture in the neodermis, which more closely resembled that of normal skin (Figure 2). The results of these studies are described in more detail elsewhere [36,45,46].

In terms of safety and toxicology testing required before ethics and regulatory authority approval of the clinical evaluation of avotermin, standard preclinical safety and toxicology evaluations required for other therapeutic areas were performed: safety pharmacology; acute- and repeat-dose exposure, genotoxicity, and reproductive toxicology; and immunological safety. When developing therapies for scar improvement, it is equally important to demonstrate that the treatment has no adverse effects on wound healing (i.e. is safe, well-tolerated and does not impair the rate or quality of normal wound healing), that systemic exposure to the product by the intended route of administration significantly exceeds that which will be used in humans, under conditions of maximal exposure and in a model that is clinically relevant. To this end, we developed an animal model in which two 20 cm full-thickness, sutured cutaneous incisional wounds were made in the Gottingen Minipig. Pigs are frequently used for toxicity studies involving dermal administration, as their skin is considered very similar to that of humans. The study showed that intradermal administration of avotermin, at concentrations considerably higher than those used in human trials, is well tolerated at the dosing site, has low bioavailability (0.1%) and no systemic toxicity. Evaluation of histological tissue sections of wounds at 28 days following wounding and treatment with avotermin showed that healing was complete in all animals in all treatment groups. Tensiometric analyses showed that intradermal avotermin at doses of up to 6000 ng/100 μL/linear cm does not adversely affect wound strength compared with placebo and no-treatment (surgical) controls. Overall, the study showed that avotermin did not result in any statistically significant ($p < 0.05$) changes in any parameter evaluated (wound healing, wound strength, or clinical pathology evaluations) compared with placebo or no-treatment (surgical) controls. Finally, it is important to note that the amino acid sequences of TGFβ3 and the cell-surface receptors through which it exerts its biological effects (TGFβ type I and II receptors) are highly conserved between humans and the preclinical species

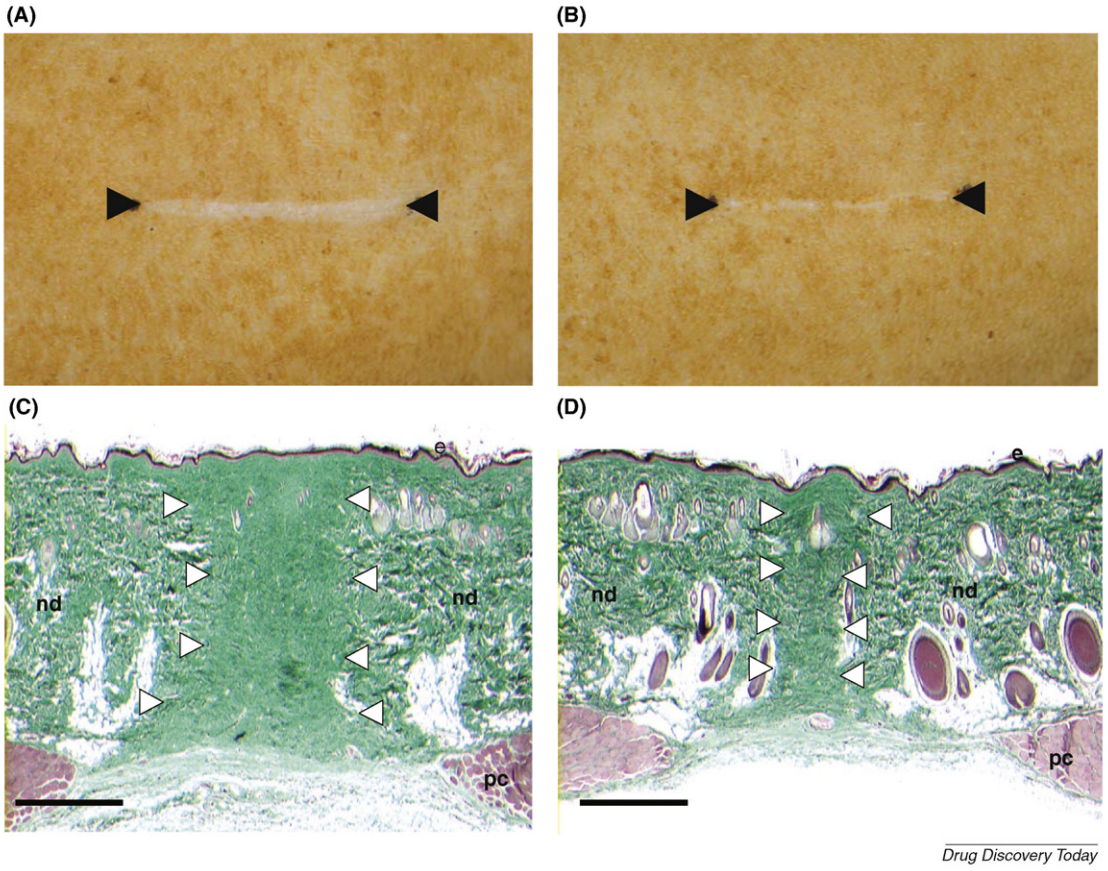

FIGURE 2

Examples of the macroscopic and microscopic scar-improving effects of avotermin. Full-thickness cutaneous incisional wounds in a rat model were treated around the time of wounding (once at the time of surgery and 24 h later) with intradermal injections of placebo or avotermin and harvested 84 days later. The macroscopic appearance of scars with placebo treatment **(A)** were comparable to no treatment (surgical controls) while those treated with avotermin at 50 ng/100 μL/linear cm of wound margin **(B)** were significantly improved showing reduced scarring (arrowheads indicate the ends of the original 1 cm wounds). Avotermin treatment **(D)** also resulted in a microscopic structural improvement of collagen within the scar such that scars were narrower and the regenerated tissue more closely resembled the normal surrounding skin/dermis compared with placebo treatment **(C)**. Placebo scars were characterized by large parallel bundles of collagen. In panels (C) and (D) arrowheads indicate the edges of scars; e, epithelium; nd, normal dermis; pc, panniculus carnosus muscle; scale bar = 500 μm.

studied (e.g. dog, pig, rat, and mouse). Between humans and these species, there is 98–100% identity in the amino acid sequence of TGFβ3 and 91–100% identity for the receptors, emphasizing the relevance and importance of the results obtained from animal studies *in vivo* to the intended clinical indications in humans.

The scar-improvement efficacy of avotermin demonstrated in preclinical models has translated into humans. To date, seven phase I/II human clinical trials in healthy volunteers have established that avotermin administered acutely (i.e. at the time of surgery) to full-thickness incisions results in statistically significant improvements in scar appearance compared with placebo and/or standard care. Avotermin has demonstrated a broad efficacious dose range, with statistically significant improvements seen with concentrations ranging from 50 to 500 ng/100 μL/linear cm wound margin. Study assessments have shown that scars resulting from wounds treated with avotermin more closely resemble the surrounding normal skin than control scars, with beneficial scar-improving effects being evident during the first months following surgery and maintained in the longer term (at 12 months and beyond). Histological examination of excised scars confirmed that collagen organization at sites treated with avotermin was markedly improved and more like normal skin compared with placebo-treated sites.

Human studies have also provided a large body of evidence on the local safety of intradermal avotermin (to date more than 1000 human subjects have been exposed). In all studies, avotermin demonstrated a favourable safety profile and while local effects were reported, these were generally mild and typically associated with the surgical procedure. Importantly, no differences were detected between drug-, placebo- and standard care-treated sites.

Using a within subject, controlled trial design, it is not possible to compare directly drug and placebo in terms of systemic safety, owing to the fact that all subjects receive both drug and placebo. The nature and incidence of 'systemic' adverse events reported in clinical trials evaluating avotermin, however, appear to be consistent with the expected incidence in the general population over an extended follow-up period (e.g. colds, headaches and so on).

In summary, the clinical studies performed to date have provided further evidence that avotermin is a new class of prophylactic medicine that promotes regeneration of normal skin and improves scar appearance following injury or surgery to the skin.

Ilodecakin (recombinant human interleukin 10; IL10; ilodecakin)
Ilodecakin was identified as a candidate scar-improvement therapy based on preclinical studies demonstrating that deletion of the IL10 gene in mice results in a worsening of scarring compared with wild-type littermates following wounding (Renovo, data on file). Further nonclinical studies in a rat model showed that intradermal adminstration of ilodecakin to incised cutaneous wounds (at the time of wounding) led to improved scar appearance compared with controls, with macroscopic improvements in scar appearance accompanied by histological improvements in dermal (collagen) architecture (Renovo, data on file).

IL10 is a major factor regulating suppression of the inflammatory response and the activity of macrophages, which play a pivotal role in the inflammatory phase of wound healing [47]. On the basis of preclinical studies, it is proposed that IL10 reduces skin scarring via the following mechanisms: (1) modulating recruitment and differentiation of inflammatory cells, and reducing their secretion of pro-inflammatory cytokines [48–50]; (2) decreasing extracellular matrix (ECM) production [51,52] and increasing ECM breakdown by upregulation of proteolytic enzymes (e.g. the matrix metalloproteinases) [53]; (3) downregulating TGFβ1 activity/expression [51,54].

Two independent published studies have provided further evidence that modulation of the inflammatory response by IL10 reduces scar formation following skin wounding in mice. The first confirmed that IL10 protein and gene expression are upregulated in incised wounds to the skin (peaking at both 3 and 72 h post-wounding), with the major sources identified as epidermal cells and infiltrating mononuclear cells [55]. Injection of a neutralizing anti-IL10 antibody inhibited the recruitment of neutrophils and macrophages to the site of injury, and the release of chemokines and pro-inflammatory mediators. The second study investigated modulation of wound healing and scarring following overexpression of IL10 [56]. IL10 was overexpressed by injecting a lentiviral vector expressing the IL10 gene into the skin of mice that, 48 h later, received an excisional wound to the skin. At 3 days post-wounding, both the inflammatory response and release of inflammatory mediators were reduced at wound sites injected with the vector overexpressing IL10 compared with those receiving the control vector (no IL10). After three weeks, wounds overexpressing IL10 showed reduced inflammation, a lack of collagen deposition and restoration of normal dermal architecture compared with the control mice. There is additional evidence that IL10 reduces collagen deposition *in vivo*, with studies demonstrating that introduction of the IL10 gene into mice decreased pulmonary fibrosis resulting from bleomycin-induced lung injury [54,57].

As with the development programme for avotermin, appropriate preclinical safety and toxicology studies of ilodecakin have been needed to support ethical and regulatory authority approval for human clinical trials. Renovo has completed one prospective, randomized, double-blind, placebo-controlled (within subject) phase II study evaluating the scar prevention and reduction efficacy of ilodecakin administered intradermally to full-thickness incisions in healthy volunteers. The trial met its primary endpoint, with intradermal ilodecakin at concentrations of 5 and 25 ng/100 μL/linear cm achieving statistically significantly improvements in scar appearance compared with controls (placebo and standard wound care) at 12 months after wounding. The tolerability of intradermal ilodecakin was good. The incidence of non-site-specific adverse events was consistent with that expected for a healthy population [58–60] and site-specific adverse events occurred at a similar low incidence at sites receiving ilodecakin, placebo or standard care.

These data once again demonstrate the translation of preclinical efficacy into humans. They confirm that ilodecakin has utility for improving human scar appearance.

Summary and perspective

Scarring following surgery or injury is difficult to predict, and both physicians and their patients are highly concerned with minimizing scar appearance and value even small improvements in scarring as clinically meaningful. While a number of treatments and regimens are used for scar management in clinical practice, there is no universally accepted treatment and no registered pharmaceuticals for the prophylactic improvement of scarring in the skin. As such, this therapeutic area is one of unmet medical need and significant opportunity. A range of therapeutic approaches have been reported as under development in the literature and, in the past few years, avotermin and ilodecakin have progressed most, with efficacy and safety demonstrated in randomized, controlled phase II clinical trials. The data generated to date with these therapeutic products demonstrate that the discovery and development of pharmaceuticals to address the unmet medical need of scarring is tractable and that avotermin and ilodecakin represent a new class of prophylactic medicines that promote the regeneration of normal skin and improve scar appearance. Finally, scarring at other body sites, organs and tissues including the nervous system (peripheral and central), tendons, the vascular system, the eye, gastrointestinal and reproductive organs, the lung, liver and kidney can cause significant clinical morbidity. Such scar reduction therapies developed for the skin may have additional utility at these sites. In support of this, reports in the literature have demonstrated significant reduction of scarring in relevant preclinical models of myointimal hyperplasia with avotermin [61,62] and in peripheral nerve injury with ilodecakin [63].

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