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Healing Chronic Wounds: Current Challenges and Potential Solutions

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Abstract

Purpose of Review: The purpose of this review is to raise awareness, examine the challenges faced by wound care researchers and explore opportunities for potential improvements.

Recent findings: Chronic wounds are associated with significant morbidity and mortality, and they represent a major medical and financial burden. Despite this, no new therapy has received FDA efficacy approval for the treatment of chronic wounds since 1997. Previous preclinical studies using animal models did not translate to human wounds due to inherent limitations of experimental models, variability in assessment methods and overall experimental design. Clinical trials continued to be challenged by the balance of the inclusion and exclusion criteria, the high cost and time expenditure of the trials, and the constraint of a single FDA-acceptable outcome of complete wound closure.

Summary: Wound research faces multiple challenges in both pre-clinical and clinical research that slowed progress and development of efficacious therapies. Solutions to such challenges will provide new opportunities for improved study design in the future.

Keywords

Chronic Wounds; Research Study Design; Clinical Trials; Translational Medical Research

Introduction:

Chronic wounds are a significant medical and financial burden on the health care system. Wounds represent 1% of all skin disease diagnoses in the United States, and account for 6.07% of all cutaneous-related deaths annually [1]. In fact, the 5-year mortality rate for diabetic foot ulcers (DFUs) and ischemic ulcers is higher than some cancers, including

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Conflict of Interest

The authors declare that they have no conflict of interest.

Compliance with Ethics Guidelines

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breast and prostate cancer [2]. Patients with chronic wounds report major negative impacts on their quality of life, with statistically significant increases in anxiety and depression and decreased perceived social support [3–7]. Beyond the morbidity and mortality, wounds are the most expensive skin ailment, with more than \$14 billion spent annually on the management of venous leg ulcers alone [8].

Due to the high morbidity, mortality, and cost, research is being undertaken to improve wound care. There are 48 studies on venous leg ulcers (VLUs) and 109 studies on DFUs currently listed as recruiting, enrolling, or active on clinicaltrials.gov [9]. Of these, there are 18 interventional phase 1 – 4 trials on VLUs and 65 phase 1 – 4 trials on DFUs (Table 1). Despite the research dollars being spent on understanding the biology and pathophysiology of wound healing as well as on the development of new treatments, and despite the large number of treatments receiving FDA approval **for safety**, very few treatments have received FDA approval **for efficacy**. In fact, since becaplermin gel was approved in 1997, no new chemical entity has been approved as efficacious by the FDA to treat chronic wounds [10]. Examining the reasons why therapeutic developments failed to receive approval over the past 20 years may offer insight into approaches to improve research protocols in the future. Herein we will discuss some of the challenges that may be contributing to such low approval rates, including study designs and working with the FDA and industry, and we will explore avenues to overcome these obstacles. While this article will focus on the U.S., the principles discussed are applicable to research communities in other countries.

Chronic wounds – the ultimate puzzle

Chronic wounds are complex on both cellular/molecular and clinical level and stymy attempts at simplification. At the cellular level, wound healing involves the complex effort of many cell types including keratinocytes, macrophages, platelets, fibroblasts, and endothelial cells that are spatially coordinated in timely fashion [11]. After injury to the skin in acute wounds, keratinocytes release pro-inflammatory signals that acts as the first alert of skin damage [12, 11]. At the same time, the clotting cascade is activated, and hemostasis is initiated. Platelets release growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), and transforming growth factor (TGF-beta). Inflammatory cells migrate to the wound site to remove tissue and bacteria. Macrophages initiate the development of granulation tissue and release a variety of cytokines and growth factors. Endothelial cells proliferate and blood vessels form with the stimulation of vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF). Epithelial cell migration and proliferation is stimulated by EGF, TGF-alpha, and FGF. Finally, once the wound has reached 100% epithelialization, keratinocytes undergo differentiation and stratification and scar remodeling commences [11].

When these highly organized and coordinated cellular processes are not properly executed or are disrupted, chronic wounds may form. In chronic wounds such as venous leg ulcers, instead of granulation tissue and new vessel formation, tiny vessels surrounded by fibrin cuffs are present [13]. The inflammatory infiltrate, instead of resolving after removal of dead tissue and bacteria, remains chronic and is composed of neutrophils with an aberrant phenotypic profile [13, 14]. Analysis of keratinocyte biology and their gene signatures in

chronic wounds indicate robust hyper-proliferative activity [13, 15]. Wound fibroblasts appear senescent and are unresponsive to growth factor signaling [11, 16, 17]. These observations indicate that chronic wounds have undergone complex fundamental changes along multiple cell types and processes. Thus, in this multifactorial system there is no one specific target point for intervention. Similarly, it is challenging to replicate it in animal model systems and to study the mechanisms that contribute to such complex pathology [18].

On the clinical level, physicians must act on multiple pathways to encourage wound healing. Optimal wound care should address the underlying condition (compression for venous leg ulcers, relief of pressure points/offloading for diabetic foot ulcers, etc.), include debridement for stimulation of the senescent tissue and removal of biofilm, management of exudate with appropriate dressings, evaluation of infection, and treatment with advanced therapies. When a single one of these factors is not appropriately addressed, patients may fail to heal. Knowing what therapy a patient needs is difficult and the standard of care varies by region [19]. Furthermore, patients with chronic wounds often have a long list of comorbidities that must be managed for optimal healing. For example, patients with diabetic foot wounds often have kidney and cardiac disease related to their diabetes. Those diseases must be controlled for optimal wound healing, and particularly in the case of patients with kidney or liver disease, there may be limits on what treatments can be safely used. Given this complexity at both the clinical and cellular level, it is not surprising that studies on wound healing have often failed to generate significant results [19].

Challenges in study design

Preclinical trials—The combination of the multifactorial biology of wound healing and the complex pathophysiology of chronic wounds makes them difficult to study. Prior to approaching clinical testing, the FDA requires preclinical evaluations of treatments for preliminary efficacy, toxicity, pharmacokinetics, and safety information. While these trials provide important information, the results vary in their translation to human conditions. For example, preclinical trials with EGF showed promising initial results [20], supporting the notion that exogenous EGF should directly stimulate keratinocytes to migrate and proliferate leading to accelerated wound closure [21]. However, human trials did not demonstrate a major clinical benefit with exogenous EGF in the US. It was discovered much later that cells in chronic wounds have very low expression of EGFR on their cell membranes, deeming the growth factor ineffective, which could not be observed in pre-clinical models but led to the low response rate seen in clinical trials [21, 16].

The reason for the poor translation of preclinical to clinical trials has a biological basis. There are clear structural differences between murine models in comparison to human skin, including different skin thickness, blood flow, and multitude of growth factor receptors [22]. Additionally, not only is there a difference in skin physiology, but the wounds in mouse models primarily heal through contraction, while human wounds close primarily through reepithelialization [22]. Pig skin is a better analog for human wound healing [23]. Anatomically, both pig and human skin have a thick epidermis, well developed rete-ridges, dermal papillary bodies, and abundant subdermal adipose tissue [23–25]. Additionally, porcine models and humans heal through physiologically similar processes that are

dependent on reepithelialization instead of contraction [23, 25]. In fact, a perspective article demonstrated that porcine model results translated to human studies 78% of the time, vs 53% and 57% for small mammal and in vitro studies respectively [23]. However, studies on porcine models are much more expensive and lack opportunity for genetic manipulations, limiting their use [22, 23]. There are some important differences between human and porcine skin, including substantial differences in the pilosebaceous systems and a less vascular dermis and hair follicle in pigs in comparison to humans [25, 24]. These significant differences in animal models in comparison to human skin contribute to challenges in translating findings from preclinical testing to the effects found in patients.

Another difficulty faced in preclinical trials is the variety of wound types induced and the lack of standardization of assessment methods of wound healing [26]. For example, the type of wounds assessed varies from excisional, splinted, magnet-pressure induced, ischemic, diabetic, aging, infected, to humanized [26]. Coupled with the equally variable multiple assessment methods that include planimetry, wound size, presence of scab, reepithelization by histology, tensile strength, cellular infiltrate, microbial composition, rate and type of inflammation, and transcutaneous water loss makes comparisons of outcomes very difficult. In addition, many studies do not report detailed aspects of their experimental wound design, making the comparative data analyses very difficult. Finally, the studies on animal models haven't historically taken into account additional important variables such as animal age, sex, microbiome, diabetes, or length of underlying condition into their study design [26–29]. These factors have been shown to impact healing in the models, and may contribute to the poor translation of preclinical animal trials to human trials [26, 29, 27].

Clinical trials—Arguably, one of the major challenges in every clinical trial is the recruitment of patients. As the variability regarding the co-morbidities of complex patients (such as diabetes and its complications, cardiovascular, psychological, etc.) along with variations of the wound itself (size, duration, position, colonization/infection, etc.) dictates relatively stringent exclusion criteria, leading to slow recruitment. Recruitment rates are often coupled with estimated costs of clinical trials, leading to a major challenge: finding the balance in inclusion criteria that would satisfy the stringency while not compromising the recruitment rate.

Finding this balance is difficult. High quality wound trials must find the “goldilocks” of wounds: those that will not heal on their own, but have the potential to heal with intervention. The exact inclusion and exclusion criteria is determined by each individual study, but the wound healing community has begun to develop criteria that are applicable across studies to determine appropriate candidates. For example, for studies on venous leg ulcers, the criteria outlined by Margolis et al. may be appropriate for screening patients [30]. This guideline categorizes VLU's based on wound size and duration to determine which subjects may be appropriate for studies. In diabetic wounds, patients are commonly considered ineligible for study on the presence or history of infection/osteomyelitis (a relatively common occurrence in clinical practice), size, and duration of ulcer [31, 32]. In addition to these standard restrictions, patients are often excluded based on the presence of comorbidities that may confound the results [33]. Using these criteria dramatically improve a wound trial's opportunity for success by isolating the wounds with the best chance of

demonstrating treatment efficacy, but also increases the difficulty of recruiting. It may be that only one out of five patients (with an already rare condition) may meet these stringent criteria.

In addition to the stated inclusion/exclusion criteria, subject recruiters may have their own subjective criteria that limit patient inclusion. A study on nurses involved in patient recruitment for wound studies indicated that they considered other factors beyond inclusion/exclusion criteria in patient selection. These factors included their personal relationships with the patient, perceived patient motivation and compliance, patient social and environmental issues, and their overall opinion of the patients' health [34]. The recruiter is trying to improve patient recruitment by finding the "perfect" patients, but they inadvertently decrease the number of eligible patients. Furthermore, the recruiter is essentially performing a pre-screening exam that may exclude key patients from the study results, and thus weaken the overall study design [34].

Study duration can also be a recruitment challenge, as patients may be unwilling to conform to the strict treatment schedules and long follow-up periods. The duration of clinical trials generally last 4–24 weeks. Patients may be required to return to clinic weekly or with even greater frequency. For patients who lack mobility, it is difficult to make each of these trial visits. Additionally, as these trials are typically randomized, patients are unsure if they are receiving the trial medication or a placebo. Given the long time commitment patients may not be willing to risk receiving a placebo in place of another known advanced treatment option. Furthermore, if patients do not improve in the first several weeks of a trial, they may withdraw, further hurting the validity of the study and slowing recruitment. While the challenges of long study duration are not unique to wound care, wound care trials cannot compensate by finding more patients as the inclusion/exclusion criteria are particularly strict.

A final difficulty in clinical study design is standardizing the standard of care. Ethically and methodologically, all wound trials must include standard of care wound healing in addition to the experimental treatment. However, standard of care is not consistent. It varies between different parts of the world, regions of the country, academic centers, and even clinics [19]. For example, compression is considered a mainstay of therapy for VLUs. However, studies evaluating compression have shown a huge disparity in results, which is believed to be due to the variance in the delivery of compression and in the populations of subjects being studied [33]. In fact, there is not only variance in the strength of compression between investigators, but also a wide range of pressures between different patients of a single bandaging physician [33]. Thus it is very difficult to standardize compression therapy as part of standard of care in clinical trials. This variability contributes to the difficulty in obtaining large multicenter datasets that are comparable.

The foregoing limitations on study design demonstrate that successful conduction of research is prolonged and difficult. These studies are expensive and require long-term financial support. When not executed precisely, there are multiple areas for confounding factors to influence the study and dilute significant results. The first step in proceeding to resolve these challenges is awareness and acknowledgment of what they are.

Working with the FDA and Industry—As pointed out previously, studies on chronic wounds are intrinsically difficult. In the case of wounds, the FDA only accepts full closure as the primary outcome [35, 36]. When experimental treatments have failed phase 2 and 3 clinical trials, the most common reason for failure is an inability to reach complete closure, despite the very promising trends and statistically significant improvements in prevention of recurrence or improvement of quality of life [37, 38, 10]. For example, topical vascular endothelial growth factor, was shown to be safe and well tolerated in clinical trials, but could not reach the endpoint of complete healing within 12 weeks [10]. Other therapies such as human keratinocyte growth factor-2 for venous leg ulcers and platelet-derived growth factor-BB for pressure ulcers did in fact show accelerated wound healing, but unfortunately did not meet the only acceptable endpoint (complete healing) and thus were not approved [38, 37]. While ideally the best wound treatment is one that closes the wound, this is not the only meaningful outcome that benefits to patients. For example, an outcome that reduces morbidity and mortality, such as a reduction in lower extremity amputations, would clearly be significant [39, 36].

More recently, there have been efforts by the wound care community to work with the FDA and update accepted outcome measures of wound treatments. A survey of wound care clinicians assessed alternative wound outcome measurements [36]. The top endpoints supported by wound care professionals included reduced pain (currently recognized as a secondary endpoint), reduced infection (currently recognized as a secondary endpoint), percent area reduction after 4–8 weeks of care, reduced recurrence, reduced amputation, reduced economic burden, improved function and ambulation, and improved quality of life (including social isolation, depression, odor, pain, and function) [36]. This study is very encouraging as it initiates the dialogue between the government and the wound healing community including patients, wound care providers, wound healing related societies, industry and insurance companies.

Beyond challenges working with the FDA, there are also challenges working with industry sponsors of major clinical trials. For example, marketing considerations may influence clinical trial design [33]. Companies aim for the largest possible market for their products and this can influence study design, as the entry criteria of these trials can affect the product's eventual label. Sponsors may broaden their inclusion criteria based on market considerations, instead of studying a discrete subset of patients most likely to benefit from the treatment [33]. Additionally, as discussed previously, the cost and time required to provide an adequate study for wounds can be significant, especially if the only accepted outcome is complete healing. This is a barrier for high quality studies, even assuming a perfect study design is determined initially. However, most studies do not have perfect initial projections, and often trials take longer and/or more expensive than initially predicted. It has been reported that randomized controlled trials often request time and financial extensions due to the difficulty in meeting the required sample size [40]. These additional costs and time constraints on clinical trials can tax the overall budget, forcing concessions in experimental design.

The future: improving outcomes of wound healing—While we have outlined some of the challenges facing wound healing research, there are multiple approaches that can

potentially improve both wound healing research methodology and improve outcomes (Figure 1). The first step is to improve standardization of preclinical testing design to support clinical development. For example, it is important to choose the appropriate model that is in line with the investigated mechanism of action. Additionally, specific details of the experimental model need to be provided so that comparative studies can be performed [26]. This will improve standardization and keep researchers accountable so the limiting factors discussed earlier such as murine age and disease don't confound study results. More helpful still would be the formation of a consensus from the basic science wound healing community on standardized approaches to preclinical testing.

The next important step is to maintain the inclusion and exclusion criteria throughout the trial regardless of the interim encouraging data. While there are incentives to relax inclusion/exclusion criteria at some point to make clinical trials faster and financially sound, this may be detrimental to the overall strength of study and impact its final outcome. Conversely, individual recruiters should not limit themselves with additional selection criteria such as the patient's environmental or social situation, as it excludes important populations from the results. Strong inclusion/exclusion criteria control for confounding variables, and thus help to improve the probability of a successful trial.

Another approach to improve wound healing research is developing strong clinical data to support multiple acceptable clinical endpoints. As a comparison, accepted endpoints for cancer research include overall survival, symptom improvement, disease-free survival, objective response rate, progression-free survival, and improvement of quality of life [10]. Meeting different clinical endpoints, such as improved 5-year survival, provides multiple avenues for approval, resulting in a plethora of available therapies [19]. In turn, this allows for combined therapeutic approaches and a higher level of customization. As we mentioned above, there is an effort currently being undertaken by the wound research community and the FDA to establish other therapeutic targets to wound healing [36]. This would allow significantly more treatment options to be approved, and would drastically improve quality of life.

Another lesson the wound healing field can adopt from cancer research is the development of biomarkers in association with wound therapies. Human epidermal growth factor receptor 2 (HER2) positive breast cancer has been found to be a marker of poor prognosis [41]. Trastuzumab is an antibody targeting HER2 cells, and is used to specifically treat cancers with the HER2 biomarker [41]. Many promising biomarkers are currently being developed that may represent diagnostic and therapeutic targets in wounds [42]. For example, quantitative assessment of matrix metalloproteinases is currently being studied as a predictor of poor wound healing [43]. Specific targeting of biomarkers on susceptible patients will allow for therapies with a more personalized approach, and help to eliminate some of the variabilities in inclusion/exclusion criteria. Recently, NIDDK launched initiative in forming Diabetic Foot Consortium that will involve multiple clinical sites in development and validation of biomarkers and additional research studies related to pathophysiology of DFUs.

Conclusion:

Wound research has faced many challenges over the past two decades, and has had few success stories in bringing new efficacious therapies to patients. Importantly, major advances have been achieved in basic and translational research regarding the wound healing process and its pathology. While wound research faces intrinsic challenges due to the multifactorial nature of healing, difficulties creating adequate preclinical models, and the expense, length, and exclusivity of the trials, these challenges can be overcome with an informed approach. The major steps necessary to improve wound research are 1) choosing the adequate and meaningful models for preclinical trials and providing necessary information for standardization, 2) maintaining inclusion and exclusion criteria during clinical testing, 3) developing clinical data to support the acceptance of the relevant primary outcomes for wound trials beyond complete wound healing, and 4) development of biomarkers and personalized medicine approaches to better determine which patients have the potential to respond to specific therapies. These changes will allow the wound community to move beyond the limitations and provide meaningful approaches for improvement in wound care in the years to come.

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Figure 1.

A summary of current challenges and potential solutions in healing chronic wounds.

Table 1.

Ongoing interventional wound trials. Results were gathered from clinicaltrials.gov using the quoted search term on May 15, 2018. Trials were considered active if they were listed as recruiting, enrolling by invitation, or active but not recruiting.

Ulcer type	Phase 1 trials	Phase 2 trials	Phase 3 trials	Phase 4 trials
<i>“Venous Leg Ulcers”</i>	3	11	3	1
<i>“Pressure Ulcers”</i>	1	2	1	0
<i>“Diabetic Foot Ulcers”</i>	22	25	11	7