

Breakthrough Technologies in Diagnosis and Therapy of Chronic Wounds

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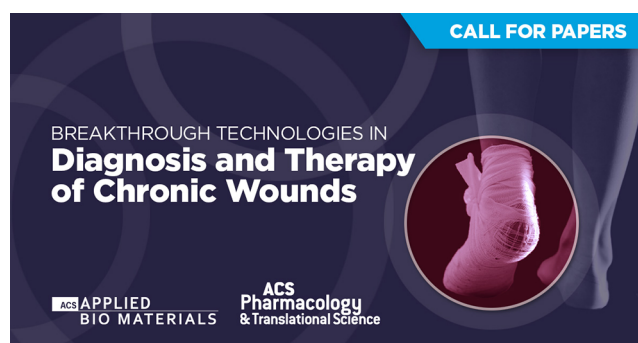
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Chronic Wounds. Wounds throughout the body are common and can be debilitating injuries with long recovery times.^{1–3} Wounds that fail to proceed through the normal phases of inflammation, proliferation/repair, and remodeling remain in a dysregulated inflammatory state and are reclassified from acute to chronic wounds.² Chronic wounds are characterized by their inability to heal within an expected time frame and are heterogeneous in pathogenesis, size, body location, likelihood of infection, and amputation risk.⁴ Various disease states result in chronic wound development, including diabetes (diabetic foot ulcers), venous insufficiency (venous ulcers), and undue skin pressure (pressure ulcers).^{1,5–7} In the United States, the prevalence of chronic wounds is estimated to be 4.5 million patients, resulting in substantial economic and psychosocial costs.^{2,8} With risk factors for chronic wounds becoming more prevalent due to increasing population age and obesity rate, the market size of wound closure products has been increasing and was projected to exceed \$25 billion USD in 2022.⁸

In clinical practice, chronic wounds are treated with initial and regular extensive debridement, to remove devitalized tissue, and the use of non-specific wound dressings.^{2,9} These commercially available wound dressings (wet gauze, hydrogels, hydrocolloids, foam dressings, films) promote wound healing by providing moisture, gas exchange, thermal insulation, drainage of exudates, a barrier against infections, and minimization of skin irritation or friction between the wound and clothing or devices such as wheelchairs.^{2,10,11} Some commercial bandages may also deliver debriding or antimicrobial agents.² More advanced commercial dressings such as acellular and cellular skin substitutes are costly and generally used in specialty settings.^{1,2,12,13} These skin substitutes provide a provisional extracellular matrix (ECM) substitute for cell anchorage, and function as a growth factor depot and, in the case of cellular skin substitutes, a stromal cell reservoir.^{1,12} Currently, the selection of the wound dressing relies on a clinical assessment of the patient's wound.² The wide variety of wound dressings combined with a general lack of high-quality evidence complicates wound dressing selection in clinical routine.^{2,11}

Emerging Targets in Chronic Wounds. In the past two decades, our understanding of chronic wound pathophysiology has deepened. It has become increasingly accepted that the inflammatory phase is likely the most dysregulated process in chronic wounds.^{1,3,14,15} Chronic wounds exhibit a chronic pro-inflammatory environment with high levels of pro-inflammatory chemokines, cytokines, reactive oxygen species (ROS),



and ECM-degrading matrix metalloproteases (MMPs).^{1,3,14,15} This pro-inflammatory environment is a positive feedback loop, as it continuously attracts neutrophils and monocytes, polarizes macrophages into the pro-inflammatory M1 phenotype, and leads to the further secretion of pro-inflammatory and leukocyte-attracting chemokines and cytokines.^{1,16} This environment impairs central processes of regeneration such as angiogenesis, granulation tissue formation, and re-epithelialization, and impairs the progression into the proliferation and remodeling phases of wound healing.^{1,16}

The chronic, low-grade inflammation in chronic wounds can be targeted by modulating neutrophil and monocyte recruitment and macrophage polarization.¹ Neutralizing pro-inflammatory chemokines and cytokines in chronic wounds breaks the cycle of leukocyte influx and secretion of leukocyte-recruiting chemokines.¹⁷ Alternatively, delivering anti-inflammatory M2 macrophages to chronic wounds improves angiogenesis and re-epithelialization.¹⁸ In diabetic wounds, recent studies demonstrated the counterintuitive hypothesis that induction of an acute inflammation can decrease chronic inflammation and improve wound healing.^{19–21} The local application of acutely pro-inflammatory molecules might also be a promising strategy for non-diabetic chronic wounds.

In addition to chemokines and cytokines, immune cells secrete other factors such as ROS and MMPs that directly impair the proliferative and remodeling phases of regener-

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ation.^{1,3,14,15,22–26} While ROS have physiological roles in wound healing, the excessive ROS concentrations observed in chronic wounds lead to lipid peroxidation, protein modification, and DNA damage.²⁴ This oxidative stress results in apoptosis of stromal cells and impairs angiogenesis, granulation tissue formation, and re-epithelialization.²⁴ To reduce ROS concentration, ROS metabolism can be modulated with small molecules. For instance, the iron(II)-sequestering agent deferoxamine inhibits the generation of the highly toxic hydroxyl radical by iron(II).²⁷ Nucleic acid therapeutics that silence genes of ROS-generating enzymes or augment the expression of ROS-degrading enzymes are also promising avenues. MMPs are endopeptidases that degrade the ECM and other substrates (growth factors, cytokines, chemokines).^{25,26} In physiological wound healing, a delicate balance in the expression of MMPs and their inhibitors leads to a controlled degradation of the ECM and enables stromal cell migration, angiogenesis, and the remodeling of the injured tissue.^{25,26} The increased MMP concentrations observed in chronic wounds leads to excessive ECM breakdown and the degradation of growth factors, which impairs angiogenesis and re-epithelialization.^{22,25,26} MMP activity can be targeted by low-molecular-weight MMP inhibitors²⁸ and nucleic acid drugs that silence MMP genes²⁹ or express tissue inhibitors of metalloproteinases. As certain MMPs are beneficial to wound healing, such as MMP8 in diabetic wounds,³⁰ high MMP subtype specificity is essential for these therapeutics. An important point to consider is the systemic bioavailability of ROS- and MMP-targeting drugs, as systemic exposure could interfere with physiologic ROS and MMP functions in other tissues.

Due to proteolysis and ROS damage, the ECM in chronic wounds is often not able to provide pro-healing cues to stromal cells and thus impairs the transition into the proliferative and remodeling phase.⁴ Polymeric ECM-mimicking dressings decorated with ECM-derived peptides promise to directly engage with and provide anchors for fibroblasts, keratinocytes, and endothelial cells.³¹ They can further provide a reservoir for the prolonged release of pro-healing growth factors.³² Compared with the clinically used skin substitutes described above, these dressings made from polymers and peptides would be potentially simpler to manufacture, more stable, and less immunogenic than biological skin substitutes.

The therapeutic targets may also become useful biomarkers that could provide insights about the prognosis of a chronic wound. As chronic wounds are classified using macroscopic and unspecific criteria (wound size, depth),³³ new molecular diagnostics are needed to understand the underlying molecular pathophysiology, make predictions on healing rate, and evaluate treatment success. Ideally, diagnostic bandages sense these biomarkers *in situ* and provide prognostic information to the clinician at the point-of-care. Biomarkers of interest include markers of inflammation, oxidative stress, MMP activity, bacterial infection, and mechanical stress.³⁴ Such molecular fingerprinting will also enable evidence-based treatment selection once molecular therapeutics become available for chronic wounds. Diagnostic wound dressings therefore promise to pave the way for personalized medicine in chronic wounds. The ultimate goal is for a bandage to sense the molecular composition of a wound and to autonomously release the right drug at the right time (theranostic wound dressing).

Scope of the Virtual Special Issue. Advances in the understanding of chronic wound pathophysiology led to the

emergence of new targets that motivate the development of diagnostic and therapeutic bandages. To highlight the rapidly evolving field of advanced bandages for chronic wounds, ACS *Pharmacology & Translational Science* and ACS *Applied Bio Materials* welcome contributions to an upcoming Virtual Special Issue, “Breakthrough Technologies in Diagnosis and Therapy of Chronic Wounds”, intended to provide readers with original research articles and review/perspective articles on transformative diagnostic and therapeutic wound dressing for chronic wounds.

The Virtual Special Issue format means that articles are published in the next available regular journal issue shortly after acceptance, instead of being published in a dedicated issue. Once all articles for the collection have been accepted, they will be featured on a dedicated web page, giving additional exposure to each publication.

The submission deadline for both journals is January 31, 2024. We are looking forward to your manuscripts and relevant pre-submission inquiries, which can be sent to the relevant journal offices at the following email addresses:

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■ Notes

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