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REVIEW

Nanobiotechnology: Applications in Chronic Wound Healing

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Abstract: Wounds occur when skin integrity is broken and the skin is damaged. With progressive changes in the disease spectrum, the acute wounds caused by mechanical trauma have been become less common, while chronic wounds triggered with aging, diabetes and infection have become more frequent. Chronic wounds now affect more than 6 million people in the United States, amounting to 10 billion dollars in annual expenditure. However, the treatment of chronic wounds is associated with numerous challenges. Traditional remedies for chronic wounds include skin grafting, flap transplantation, negative-pressure wound therapy, and gauze dressing, all of which can cause tissue damage or activity limitations. Nanobiotechnology — which comprises a diverse array of technologies derived from engineering, chemistry, and biology — is now being applied in biomedical practice. Here, we review the design, application, and clinical trials for nanotechnology-based therapies for chronic wound healing, highlighting the clinical potential of nanobiotechnology in such treatments. By summarizing previous nanobiotechnology studies, we lay the foundation for future wound care via a nanotech-based multifunctional smart system.

Keywords: nanobiotechnology, chronic wound healing, scaffold systems, cell-carrying systems, stimuli-responsive systems

Introduction

The skin is the largest organ in the body, accounting for 15% of the total body weight. It is the first line of defense against physical, chemical, and biological factors.[1,2] In some cases, the anatomical structure and biological function of the skin are impaired due to internal (local blood obstruction, inflammation, or underlying diseases) or external factors (mechanical injury, chemical corrosion, electric injury, or thermal injury).[1,3]

After damage, skin can self-heal, and this process involves four phases: hemostasis, inflammation, proliferation, and remodeling (Figure 1).[4,5] In the first few minutes after skin damage, the platelets accumulate around the wound and get activated, forming a scab to preventing bleeding.[6] After 2–3 days, the inflammatory phase starts around the wound, and the immune cells remove the dead and devitalized tissues and prevent microbial infections.[4] The proliferation phase occurs after the inflammation phase, and it is characterized by the activation of keratinocytes, fibroblasts, endothelial cells, and macrophages, which contribute to wound closure, matrix formation and angiogenesis.[7] In the 12 or more months after the primary repair is completed, the regenerated skin tissue is remodeled. During this phase, the processes activated after injury slow down, and the healed wound reaches it maximum mechanical strength.[4,5]

However, in some cases, the skin's self-healing property is inadequate, leading to the formation of chronic wounds. Chronic wounds are defined as wounds that remain unhealed even after 12 weeks.[8] The main factors delaying wound repair include diabetes, infections, and long-term inflammation. Diabetic mellitus damages the microenvironment of skin tissue, which is involved in wound regeneration. It causes increases in reactive oxygen species (ROS) levels and poor

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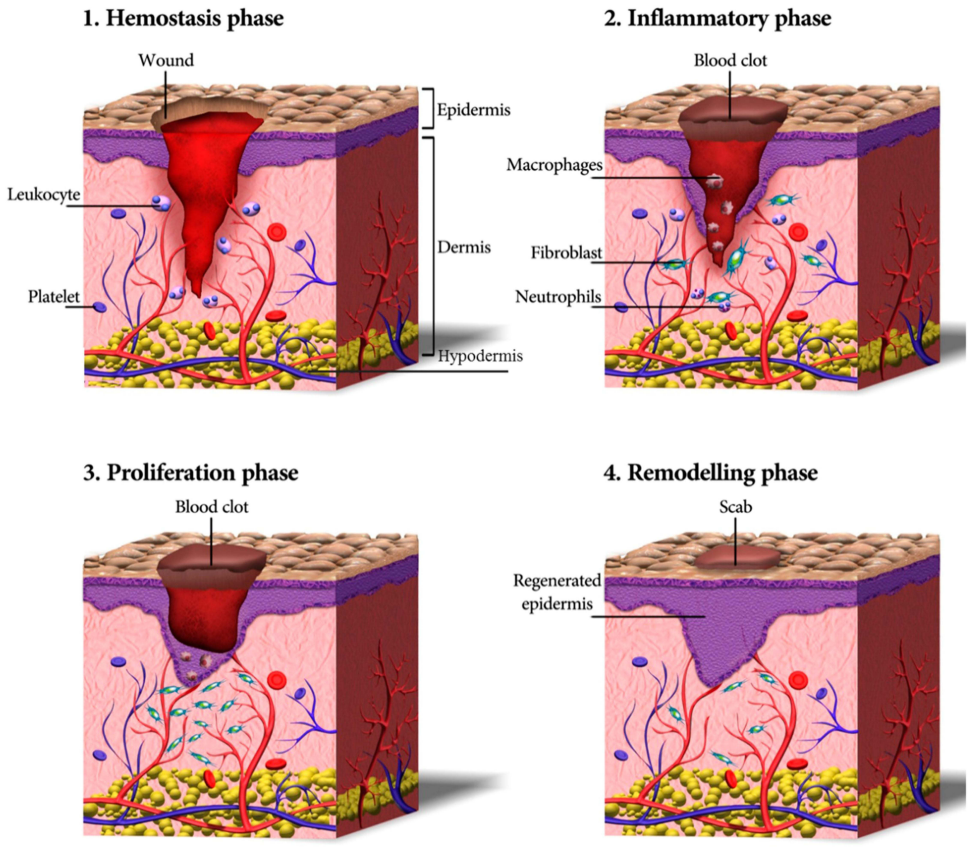

Figure 1 Phases of wound healing, including the hemostasis, inflammatory, proliferation, and remodeling phase.
Notes: Reprinted from: Tavakoli S, Klar AS. Advanced Hydrogels as Wound Dressings. *Biomolecules*. 2020;10(8):1169. doi:10.3390/biom10081169.[5] © 2020 by the authors. Licensee MDPI, Basel, Switzerland. Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).

collagen deposition.[9–11] The hyperglycemia weakens the functions of fibroblasts, keratinocytes, endothelial cells, and stem cells or progenitor cells involved in wound healing.[12] Microbial infections deplete the energy and cells required for tissue regeneration, and the bacteria can form biofilms that display antibiotic resistance, immune evasion, and wound adherence.[13,14] In unhealed skin, excess inflammation also contributes to wound chronicity owing to its cytotoxic effects and the induced tissue damage, both of which delay wound healing.[15–17] Traditionally, the chronic wounds are treated with wound dressing made of gauze, skin grafting, or even flap transplantation. Moreover, targeted antibiotics are administered in case of infection. However, Surgery for chronic wounds can be challenging due to limited donor sites, donor damage, scar formation, and even severe functional and psycho-social disorders.[18–20] Moreover, antibiotic overuse can lead to drug resistance, creating new problems for infectious chronic wounds.[21,22] Moreover, chronic wounds become refractory due to infections, diabetes, ischemia, over-degradation of collagen, and other factors, leading to the failure of traditional treatment methods. Thus, novel methods for treating chronic wounds need to be explored.

Skin wounds are the most common type of tissue injury, and they can be caused by trauma, surgery, burns, chronic diseases, or cancers.[4,23] Under adverse conditions, wounds often turn chronic. The acceleration of wound repair and improvement of the healing process are the primary objectives of chronic wound treatment. Nanobiotechnology, which involves the use of nano-sized particles in biological systems, represents the convergence of several scientific fields, including chemistry, biology, physics, optics, mechanics, and nanoscale Science and technology. Nanobiotechnology can provide tools and technologies for examining and modulating biological systems.[24,25] By applying nanotechnology in the field of bioMedicine, several novel biomaterials, biosensors, and bio-therapies have been designed and studied. It is believed that the combination of nanotechnology and biology can aid in wound management, monitoring, and repair.[26,27] Initially, the application of nanobiotechnology in chronic wound treatment was focused on the provision of scaffolds for cell migration and the replacement of traditional gauze dressing.[28–30] However, with the development of nanotechnology

and our understanding of wound healing mechanisms, various nanobiotechnology-based wound-treatments systems — including drug and gene delivery platforms, antimicrobial systems, and cell-carrying systems — have been developed and found to have prospective applications.[31–36] Nevertheless, despite these advances, wound dressings remain largely primitive and lack functions that allow wound monitoring and dynamic wound responses. Therefore, smart hydrogels or bandage systems developed using nano-sized biomaterials, which can respond to stimuli or monitor the status of chronic wounds, have been examined.[37,38]

This review article provides a summary of nanobiotechnology-based scaffold, delivery, antimicrobial, cell-carrying, collagen modulating, stimuli-responsive, and wound monitoring systems for chronic wound healing. Further, the prospects of nanobiotechnology to achieve better treatment outcomes for chronic wounds are discussed.

Nanoplatforms Designed for Chronic Wound Healing

Physiologically, the wound healing process is affected by several factors, including gene expression; cell functions such as migration, proliferation, and differentiation; the skin microenvironment; infection; ischemia–hypoxia; inflammation; and collagen formation and arrangement.[1,3,17,39–42] These factors are used as references for the design of nanobiotechnology systems that promote chronic wound repair (Figure 2) and need to be carefully considered before designing such systems.

To repair tissue defects in the wound area, a platform for cell adhesion, migration, and proliferation — ie, a scaffold for cells — needs to be established. Such a scaffold can also serve as a platform for multi-functional modification. Given their good biocompatibility, angiogenic capacity, and biomimetic behavior to natural human skin, nano-scaffold systems are widely used in tissue engineering.[43–46]

Tradition treatment methods for chronic wounds that show delayed Union involve local or systemic drug administration. However, the performance of these drugs is suboptimal owing to limitations such as low solubility and low bioactivity. Nanobiotechnology has thus been leveraged for the development of drug, gene, and exosome delivery systems that can help in overcoming these limitations.[34,47,48]

Infections, which impede tissue repair, should receive careful attention in chronic wound treatment. Silver nanoparticles, a product of nanobiotechnology, have been used clinically in the treatment of microbial infection for decades. Moreover, several more recent studies have explored new nanoplatform-based anti-infection therapies, including potential anti-infection nanoparticles (NPs).[49–52]

Cell therapy, especially stem cell therapy, is currently a focus in regenerative medicine and diabetic wound repair. In some basic medical and preclinical studies, chronic wound treatment with stem cells has shown excellent outcomes.[53–55] However, despite its great potential, the clinical translation of stem cell therapy for chronic wound healing is hindered by the lack of appropriate methods for cell encapsulation and transplantation. Thus, the development of nanobiotechnology-based cell-carrying systems can provide improved therapeutic effects.[56,57]

With the development of precision medicine, therapeutic systems that monitor wounds and respond to individual stimuli are expected to become popular. One such system is based on ferrihydrite NPs, which can respond to blue light and are effective for antimicrobial and wound healing treatments.[58] More stimuli-responsive materials and monitoring systems for chronic wound healing can be generated through nanobiotechnology.

Nanoplatforms for Chronic Wound Healing

Scaffold Systems

The term scaffold system generally refers to materials that can integrate with living tissues and cells and can be implanted into different tissues where they supplement natural tissue function based on specific conditions. In order to enable seed cells to proliferate and differentiate, a scaffold composed of biological materials that acts as an artificial extracellular matrix (ECM) is required. Scaffolds are critical for tissue engineering systems, including those for bone, cartilage, blood vessels, nerves, skin, and artificial organs (eg, liver, spleen, kidney, and bladder).

Nano-scaffold systems aimed at chronic wound healing need to possess certain important features.

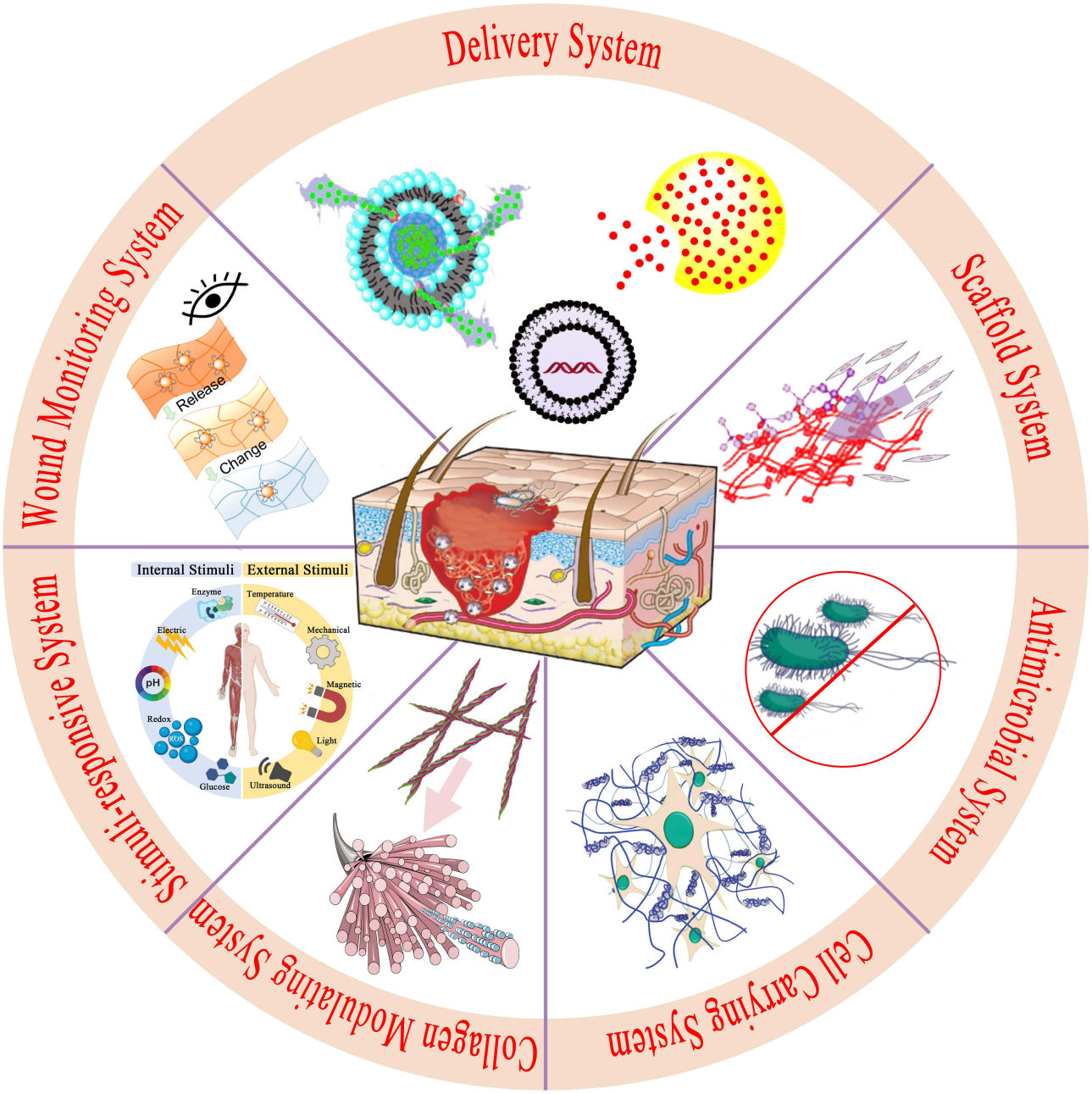

Figure 2 Nanoplatform for chronic wound healing.

1. Safety and good biocompatibility: Scaffolds should be safe. Furthermore, their chemical components and degradation products should cause minimal immune or inflammatory responses in the body during a predetermined period.[59]

2. Appropriate size, dimensions, and mechanical strength: The chemical features of the scaffold should provide suitable microenvironments and maintain the biological activity of loaded cells or tissues for a long time.

3. Appropriate pore size and distribution: Scaffolds should have a highly and well-connected porous structure with an ideal pore size to allow cells, drugs, and bioactive molecules to get evenly distributed throughout the scaffold.[60]

4. Excellent biological behaviors: Scaffolds and the substances present in the scaffold should promote the proliferation and migration of fibroblasts, keratinocytes, and endothelial cells, thus promoting wound healing.[61,62]

Table 1 Sources of Nanocomposites

Category	Examples
Natural biomaterials	Chitosan,[65] gelatin, agar, glucan, hyaluronic acid,[66] collagen,[67] silk fibroin, alginate
Synthetic biomaterials	PEG-based nano-scaffold,[68] alginate-polycaprolactone (PCL), electrospun membranes,[69,70] polyurethane-based scaffold,[71] microporous annealed particle scaffold[72]

5. Appropriate wound healing environment: The scaffold system should be able to absorb the wound exudate and prevent wound dehydration, reducing surface necrosis on the wound.[63,64]

Scaffold systems can be classified as follows based on the source and function of the materials.

Source of Materials

When designing scaffold systems for chronic wound, an appropriate matrix source needs to be selected. Table 1 lists a few sources of nanocomposites used in wound dressing. Natural nanomaterials and their derivates have good biocompatibility and can be degraded by enzymes or water. However, their characters and quality differ from batch to batch and cannot be standardized. In contrast, synthetic biomaterials, such as polyethylene glycol (PEG) nano-scaffolds, show more stable structural properties and can be chemically modified. However, the biosafety of synthetic materials needs to be strictly examined.

Function of Materials

According to their functions, tissue engineering materials can be used for bones, nerves, blood vessels, skin, and other tissues (eg, tendon, ligament, cornea, liver, and kidneys).

Tissue engineering scaffolds for the skin can be of several types. These include natural polymers (chitosan, hyaluronic acid, and collagen), nanocomposite scaffolds (eg, nanobioactive glass and metal NPs), and conducting polymers (eg, polyaniline, polypyrrole, and polythiophene).[73–75] Taghiabadi et al synthesized an intact amniotic membrane-based scaffold for cultivating adipose-derived stromal cells (ASCs). By ASCs on an acellular human amniotic membrane (HAM), they created a neoteric skin substitute.[76] Zhang et al designed a conductive and antibacterial hydrogel based on polypyrrole and functionalized Zn–chitosan molecules for the management of infected chronic wounds. They demonstrated the promising potential of the hydrogel in promoting the healing of the infected chronic wound after electrical stimulation. Currently, other tissue engineering scaffolds such as calcium phosphates and composite materials (eg, hydroxyapatite, β-tricalcium phosphate, and whitlockite) for bone tissue engineering and amniotic membranes for corneal tissue engineering are under research.[69,77]

Skin tissue engineering scaffolds can be categorized as porous, fibrous, microsphere, hydrogel, composite, and acellular materials.[73] Typically, natural biomaterials and their derivatives are biodegradable, absorbable, and harmless to the body, but their strength and processing performance are poor and their degradation speed cannot be controlled. Hence, in order to improve the mechanical and biological properties of scaffolds (eg, adhesion, strength, processing performance, and degradation speed) and accelerate wound healing, composite scaffolds have been developed by combining the characteristics and advantages of different materials. Depending on their constituents, these composite scaffolds can achieve specific functions. Currently, most novel scaffolds being developed use composite materials to obtain multifunctional characteristics.

Delivery Systems

Delivery systems are used to deliver drugs, cells, genes, and other neoteric bioactive molecules to the body or target area via transplantation or injection.[78] Traditionally, delivery systems are broadly divided into two categories, drug delivery and cell delivery. With continuous Innovation in scientific research, new approaches, including gene delivery and the delivery of bioactive molecules such as growth factors, proteins, and peptides, are being developed.

Recently, there has been a significant increase in new biotechnology-based treatments, among which cell and gene therapies are quite sophisticated. Exosomes have shown superior therapeutic potential against various conditions, and

delivery methods are being devised to maximize their therapeutic effectiveness. Moreover, exosomes are also emerging as a delivery system for other substances (eg, small molecules and miRNAs).[79] NPs are essential for the delivery of these refined substances. In addition to serving as delivery vehicles, NPs can also act as diagnostic and therapeutic agents for some diseases.[80] Research on nanoparticle-based drug delivery has mainly been focused on targeted drug delivery, and especially tumor-targeted drug delivery.[81]

Drug Delivery

A drug delivery system serves as a vehicle for therapeutic molecules. It allows drug delivery in the body, improves drug efficacy, and allows safe and controlled drug release.

The conventional routes for drug delivery[80] are gastrointestinal drug delivery (eg, oral and rectal), parenteral administration (eg, subcutaneous, intramuscular, and intravenous injection) and topical administration (eg, percutaneous injection and wound dressings). Novel drug delivery systems for wound healing can be classified into the following categories: NPs, microcarriers, and tissue-engineered scaffolds.[82] Skin tissue engineering scaffolds have been introduced earlier in this review, and NPs and microcarriers will be introduced in detail here (Table 2).

Drug-loaded nano-scaffolds that promote wound healing after topical administration have been developed. However, due to their poor solubility, short half-life, and other drawbacks, some drugs do not accumulate at an optimal concentration at the wound site for a long duration.[83] Nano-scaffolds with varying porous structures can be used to load drugs or bioactive molecules, and the porous structure can provide a breathable environment for the wound.[84] NPs carrying poorly soluble drugs are widely used to prepare controlled drug delivery systems. Nano-scaffolds typically show slow degradation, allowing long-term drug release and thereby maintaining an ideal concentration of the drug in the plasma.[85] Shamloo et al developed polyvinyl alcohol (PVA)/chitosan/gelatin hydrogels to overcome the short half-life of basic fibroblast growth factor (bFGF). The biocompatibility of the hydrogel supported the continuous delivery of bFGF and significantly accelerated wound healing.[86]

Table 2 Drug Delivery Systems Developed Using Nanotechnology

Category		Examples
NPs	Inorganic NPs	Metal nanoparticles: CuNPs,[87] AgNPs,[88,89] and Cerium Oxide NPs[90]
		Carbon-based NPs[91,92]
		Quantum dots: self-assembled GQDs,[93] Orange-emissive carbon quantum dots[94]
	Organic NPs	Dendrimers: act as antibacterial agents[95,96]
		Hydrogels: chitosan,[97] PVA,[98] and PEG[99]
		Nano-emulsions can improve the solubility and reduce the enzymatic hydrolysis of drugs[100]
		Liposomal NPs: solid lipid NPs[101,102] and nanostructured lipid carriers[103,104]
	Polymer NPs	PCL,[69] PEG,[68] and photothermal NPs[105]
Smart stimuli-responsive nanostructures		MMP9-responsive,[106] pH-responsive,[107] immune responsive,[72] and thermosensitive nanostructures[99]
Nanofibers (NFs)		NFs can increase the transfer of various molecules and perform diverse functions[108]
Microspheres coated with nanocomposites		PCL microspheres,[86] chitin microspheres,[109] bacterial cellulose microspheres,[110] and gelatin microspheres[111]
3D-printed scaffolds		Typical three-dimensional porous matrix[112]
Engineered films		Agar-glycerol-sericin films[113,114]

Abbreviations: GQD, graphene quantum dots; MMP, matrix metalloproteinase.

During the treatment of chronic wounds, the drug is usually applied directly on affected region. Nanotechnology-based drug delivery systems could enable controlled drug release. Meanwhile, the degradability and stability of the drug could also be modified using nanosystems. Hence, these drug delivery systems could improve treatment compliance among patients with chronic wounds by reducing the application frequency and the cost of treatment.

It is widely acknowledged that metal ion-based biomaterials exhibit promising antimicrobial activity when applied to wounds, making them very suitable for the management of diabetic wounds, which are prone to infection. Given their reducing properties, under oxidative stress, cuprous ions provide a promising therapeutic option for diabetic wounds. Copper ions have also been reported to promote angiogenesis.[115–117] Equipped with infrared absorption and efficient heat generation abilities, semiconductor cuprous sulfide (Cu_2S) NPs are widely employed as photothermal agents. Wang et al utilized the photothermal effect of Cu_2S and the angiogenic effect of Cu ions to prepare electrospun fibers containing Cu_2S NPs, achieving a combination of advantages based on the components and successfully promoting diabetic wound healing. Moreover, their biomaterial could also effectively inhibit the growth of skin tumors both in vivo and in vitro.[70] This system demonstrated the effectiveness of bifunctional tissue engineering biomaterials, providing a novel method for drug delivery for the treatment of biological conditions.

Gene Delivery

Classic gene therapy generally involves the expression of exogenous genes or the silencing of target genes via viral or non-viral delivery.[118,119] In general, gene delivery via viral transfection may be carcinogenic.[119] Most gene therapies for diabetic wounds are based on siRNAs. Gene therapy has become a promising strategy for the treatment of various diseases, and its effects are mediated via the regulation of RNA and protein expression.[120] Many unmodified gene therapy agents, such as proteins, peptides, and nucleic acids, are rapidly degraded or eliminated from systemic circulation before they can accumulate at effective concentrations at the target site. Owing to poor pharmacokinetics, repeated administration is warranted. This, in addition to the narrow range of safe doses, often leads to adverse effects during treatment.[121]

Several studies on wound management and especially chronic diabetic wound management have focused on gene- or RNA-based (eg, mRNA, microRNA, circRNA, and lncRNA) therapies.[122] Subcutaneous local injections can be used to directly deliver RNAs or proteins to the wound site.[123] However, due to the short half-life of the therapeutic agent, repeated administration is required, often leading to pain and poor treatment compliance. Drug delivery systems not only solve these problems but also protect gene-related small molecules from degradation and eliminated from the body. The greatest challenge in gene therapy is ensuring the successful transduction or transfection of target genes into host cells by crossing extracellular and intracellular barriers. Therefore, the engineering of gene delivery vehicles is complex.[118] Moreover, the materials used to encapsulate gene-related small molecules are required to have low toxicity and promote a high transfection efficiency.[124] Currently, the NPs that deliver siRNAs to promote wound management are composed of lipids, polymers (eg, chitosan, PEG), hyperbranched cationic polysaccharides (HCP), and silicon.[125–130]

Shaabani et al developed layer-by-layer self-assembled siRNA-loaded gold NPs with two different outer layers — Chitosan (AuNP@CS) and Poly L-arginine (AuNP@PLA).[126] They compared the two types of NPs, which had a similar core structure. They found that the two polymers had different escape mechanisms: the buffering capacity of chitosan resulted in endosome disruption,[131] while PLA bound to the endosome lipid bilayer and promoted escaped through pore formation. Their results indicated that an outer layer of PLA allows the endosomal escape of siRNA, thus improving transfection efficiency and delivering target molecules to promote diabetic wound healing. Given that naked siRNAs are easily eliminated from the body, Li et al and Lan et al designed four HCP derivative-based vehicles[128,129] for the delivery of siRNA against MMP9. This treatment led to the knockdown of MMP9, which prevents the healing of diabetic wounds, and thus promoted diabetic wound healing. Currently, nanocomposite-based gene delivery applications are focused on siRNA. However, efforts to deliver other products such as miRNA, lncRNA, or even DNA will be required in the future.

Exosome Delivery

Exosomes are endosome-derived vesicles (30 to 150 nm in size) secreted by a variety of cells, including adipose stem cells (ADSCs), bone marrow stem cells (BMSCs), and mesenchymal stem cells (MSCs).[132,133] Different types of cells secrete exosomes with different specific markers, which account for their specific functions. Despite their different origins, exosomes have a similar appearance and size and often have a common composition. Once they are isolated from an extracellular medium or from biological fluids, the source of exosomes cannot be ascertained of.[134] Exosomes can be employed as small molecules for wound treatment. The combination of exosomes with porous NPs can increase therapeutic effects while maintaining the advantages of a scaffold. Importantly, exosomes can also be used as nanocarriers for drug delivery and targeted therapy, and these are called engineered exosomes.[133,135]

Exosomes can effectively promote diabetic wound healing.[136,137] Shiekh et al embedded ADSC-derived exosomes (ADSC-exo) into antioxidant polyurethane scaffolds to achieve sustained exosome release. Their nanosystem leveraged the advantages of the scaffold, including antioxidant and antibacterial effects, to accelerate diabetic wounds healing both in vivo and in vitro.[71] To prolong the half-life and lower the clearance rate of exosomes, Lei et al designed an ultraviolet-shielding nano-dressing based on polysaccharides that allowed exosome delivery and had self-healing, anti-infection and thermo-sensitive properties.[61] These findings indicate that exosomes can be stabilized and well-delivered to target cells by combining them with porous NPs or nanocarriers and can be applied for treating chronic wounds.

Antimicrobial System

It is widely accepted that infection is an important factor to monitor during the wound healing process as it can lead to progression of the chronic wound or even sepsis.[138–140] Conventional prevention and treatment approaches for wound infection involve local or systemic antibiotic administration, which can lead to failed anti-infection treatment or even antibiotic resistance.[141,142] Several nano-formulations that have antimicrobial ability have been developed and used in anti-infectious wound therapy, playing a critical role in infection management. Table 3 lists some antimicrobial nanobiotechnology-based systems used in wound healing.

Inorganic Nano-Antimicrobial Materials

Metals have been used as inorganic antimicrobial agents for thousands of years and were even used as anti-infection agents in ancient Persia.[162] Metal NPs, such as AgNPs, AuNPs, and CuNPs, have attracted great attention due to their anti-infection properties and low toxicity.[163] Given that metal NPs do not cause antimicrobial resistance and release metal ions or produce ROS — which can kill microorganisms — they appear to be suitable alternatives to antibiotics as.[164,165]

AgNPs, which are the more well-known metal NPs, have been used widely in clinical practice and basic medical research. Wound treatment products containing AgNPs have been commercially available for decades.[166] AgNPs can continuously generate Ag^{+}, which reacts with proteins and nucleic acids, causing molecular defects and killing bacteria and viruses.[167–170] Several studies have shown that AgNPs have good potential as antiseptics. Luna-Hernández et al found that a combination of functional chitosan and silver nanocomposites showed antibacterial effects against *S. aureus* and *P. aeruginosa* in burn wounds.[152] Moreover, in mice treated with the composite dressing, silver accumulation was found to be far lower than that in mice treated with the clinically used Acasin™ nanosilver dressing. Zlatko et al demonstrated that the AgNPs hydrogel serves as a versatile platform, with features such as antibacterial efficacy, exudate absorbance, low cost, biocompatibility, hemocompatibility, and improved healing for chronic wounds.[171] Huang et al constructed an organic framework-based microneedle patch containing AgNPs. The product showed transdermal delivery and could prevent *S. aureus, E. coli*, and *P. aeruginosa* infections in diabetic wounds.[172] In addition, several commercialized products containing AgNPs have been developed for clinical treatment. These include Acticoat™, Allevyn® Ag, Aquacel® Ag Surgical, Atrauman Ag, Biatain® Silicone Ag, Flaminal®, Mepilex® Transfer Ag, SILVERCEL™, and Urgo Clean Ag.

Nano-sized gold is also useful as an anti-infection agent. It has been confirmed that AuNPs bind to bacterial DNA and show bactericidal and bacteriostatic properties.[173,174] Some studies show that Au nanocomposites can kill MRSA and *P. aeruginosa* through photothermal effects and could promote wound closure.[150,175]

Table 3 Nanomaterials Used in Anti-Microbial Wound Dressing

Components	Size (nm)	Target Pathogens	Wound Type	Ref
Ag/Fe_3O_4 NCs	15–50	*S. aureus*	Chronic wounds	[143]
AgNPs	14–54	*S. aureus* and *P. aeruginosa*	Acute and diabetic wounds	[144]
AgNPs	3–5	MRSA	Infectious wounds	[145]
AgNPs/ZnO	50	*E. coli* and *S. aureus*	Normal wounds	[146]
Au/Ag NRs	50	*E. coli* and *MRSA*	Normal wounds	[147]
Au/Ag/Cu_2O NSs	10–73	*E. coli* and MRSA	Infectious and chronic wounds	[148]
AuNCs	2	*E. coli* and *S. aureus*	Normal wounds	[149]
AuNPs	34	*S. aureus*	Infectious and burn wounds	[150]
Carbon NTs	150–250	*Mycobacterium tuberculosis*	Secondary wounds	[151]
Ag nanofilms	7–33	*S. aureus* and *P. aeruginosa*	Thermal burn wounds	[152]
CuNCs	30	*E. coli* and *S. aureus*	Normal wounds	[153]
CuNPs	110	*B. subtilis, P. aeruginosa, S. aureus*, and *E. coli*	Normal wounds	[154]
Cu_2WS_4 NCs	20	*E. coli* and *S. aureus*	Normal wounds	[155]
Cu-TCPP(Fe) nanosheets	3–5	*E. coli* and *S. aureus*	Normal wounds	[156]
Fe_3O_4	20	*E. coli* and *S. aureus*	Infectious wounds	[157]
Zn/SiO_2 nanospheres	80–120	*E. coli*	Normal wounds	[158]
ZnO	20	*E. coli* and *S. aureus*	Normal wounds	[159]
ZnO/Au NPs	20–50	*S. aureus* and MRSH	Normal wounds	[160]
ZnO NPs	20	*E. coli* and *S. aureus*	Infectious and burn wounds	[161]

Abbreviations: MRSA, multi-drug resistant *S. aureus*; MRSH, multi-drug resistant *S. haemolyticus*; NC, nanocomponent; NT, nanotube.

Compared with gold and silver, copper is less expensive and more easily available. CuNPs are considered the best candidates for developing future technologies for the management of infectious and communicable diseases.[49] Cai et al developed a CuNP-embedded hydrogel that accelerated wound healing and showed effective antibacterial capacity against both gram-positive and gram-negative bacteria as well as great photothermal properties.[176]

Inorganic non-metal nano-materials have been also considered potential antimicrobial agents owing to their intrinsic anti-infection effects.[177] Based on the unique structural and physio-chemical properties of carbon nanomaterials, a research team prepared a carbon nanofiber platform that inhibits the growth of *E. coli* and MRSA.[178] In this study, CuNPs and ZnNPs were asymmetrically distributed in carbon NFs grown on an activated carbon fiber substrate using chemical vapor deposition (CVD). The carbon NFs platform inhibited the growth of gram-positive and gram-negative bacterial strains with superior efficiency than simple metal NPs. Another study showed that carbon nanotubes can be used to prepare wound-repairing bandages with infection-preventing properties.[179]

Organic Nano-Antimicrobial Materials

The natural organic biomaterial chitosan and its derivatives are popular in biomedicine. Chitosan possesses good biocompatibility, antimicrobial properties, and low immunogenicity.[180] Using nanobiotechnology, Ganji et al fabricated a nanofiber with chitosan-encapsulated nanoparticles loaded with curcumin for wound dressing. The electrospun chitosan-based nanofiber inhibited the growth of *E. coli* and MRSA by 98.9% and 99.3% in infected wounds in mice.[50] Another type of chitosan nanofiber also showed potential in wound care owing to its antibacterial and re-epithelialization-promoting effects.[181] Antibiotic-loaded chitosan nanofibers have also been used for local drug delivery and wound treatment.[182] Other metal–organic framework nanorods have also shown bacterial inhibition in infectious wounds.[183] Dias et al developed a series of soluble potato starch nanofibers sized 70–264 nm. They incorporated

carvacrol during the synthesis of the potato starch nanofibers, and the obtained nanocomposites showed great anti-pathogenic activity against *S. aureus, E. coli, L. monocytogenes*, and *S. typhimurium*, highlighting their potential as agents for wound dressing.[184]

With respect to organic nano-materials, anti-infection approaches focus on natural antibacterial compounds such as chitosan and its derivatives. Further, owing to the bactericidal effects of metals, metal-organic frameworks are also used. Given that metal NPs are associated with the potential risks of metal deposition, organic nano-antimicrobial materials, especially natural macromolecules with antibacterial properties, may become useful for wound dressing.

Anti-Biofilm Systems

Biofilm, which are made up of surface-attached groups of microbes, are considered to be the primary cause of chronic wounds owing to their role in antibiotic resistance.[141,185–187] Most biofilms are formed on the surface of wounds. However, some special biofilms can get implanted into the deep layers of skin tissue, making traditional diagnose and treatment challenging.[188] The clinical treatment of biofilms in wounds involves wound cleansing with polyvinylpyrrolidone or hydrogen peroxide, debridement, refashioning of wound edges, dressing, and the topical or general administration of antibiotics.[189] With further insights into the mechanisms of biofilm formation and developments in nanobiotechnology, nanomaterials effective for biofilm therapy have been developed.

Nanomaterials based on metals or metal oxides are widely used against wound biofilms, including silver, copper, gold, titanium, zinc oxide, magnesium oxide, copper oxide, and iron oxide.[190,191] Owing to the small size of these particles, metal or metal oxide NPs can move across bacterial membranes and rupture them. They can destroy enzyme activity and the respiratory chain in bacteria. It has been demonstrated that Ag NPs and silver oxide NPs are the most effective against microbial biofilms.[192,193] Abdalla et al functionalized nano-silver with lactoferrin and incorporated them in a gelatin hydrogel, generating a dual-antimicrobial action dressing for infectious wounds and maximizing the anti-biofilm property of silver.[194]

Chitosan, bacterial cellulose (BC) and other natural antimicrobials have been modified using nanotechnology to treat wound biofilms. Owing to the positive charge on the polymeric chain of chitosan, chitosan NPs easily adhere to the negatively charged microbial membrane, triggering changes in permeability and preventing biofilm formation.[195] Zemjkoski et al obtained chitosan NPs through gamma irradiation and encapsuled them into BC to form BC-nChiD hydrogels with excellent anti-biofilm potential. These hydrogels could provide a 90% reduction in viable biofilms and a 65% reduction in biofilm height.[196] Mahtab reduced the amount of bacteria in a planktonic condition by treating bacterial biofilms with photodynamic therapy using curcumin encapsulated into silica NPs. After exposure to blue light, ROS was produced owing to the photodynamic properties of silica NPs. The ROS damaged biofilms, and the curcumin released prevented bacterial growth.[197]

The size of nanoparticles can be controlled, and they have a large specific area, can penetrate bacterial membranes, and show bactericidal properties. Hence, nanotechnology has great potential in destroying biofilms and treating infectious chronic wounds. In addition to providing nanoparticles with anti-infection properties, nanotechnology could also be used to provide a platform for antibiotics, enhance their solubility, prolong their half-life, and reduce the required treatment dose.

Cell-Carrying Systems

Due to its superiority with respect to tissue engineering, cell-based therapy is extensively used for chronic wound treatment.[198–201] Stem cells derived from bone marrow, the umbilical cord, and adipose and cutaneous tissue can differentiate into various tissue types and modulate cell migration, collagen deposition, re-epithelialization, and tissue remodeling.[198,202–205] Nanofibers prepared using electrostatic spinning are widely used for scaffolding. Mao et al prepared polycaprolactone nanofibrous scaffolds and combined collagen with bioactive glass NPs (CPB nanofibrous scaffold). The CPB nanofibrous scaffold exerted positive effects as a cell-carrying system containing epithelial progenitor cells (EPCs). The EPC-carrying CPB bioactive complex promoted wound healing by enhancing cell proliferation, granulation tissue formation, re-epithelialization, and cell adhesion (Figure 3).[206] Khojasteh et al found that curcumin-carrying chitosan/poly(vinyl alcohol) nanofibers can carry pad-derived mesenchymal stem cells and show excellent

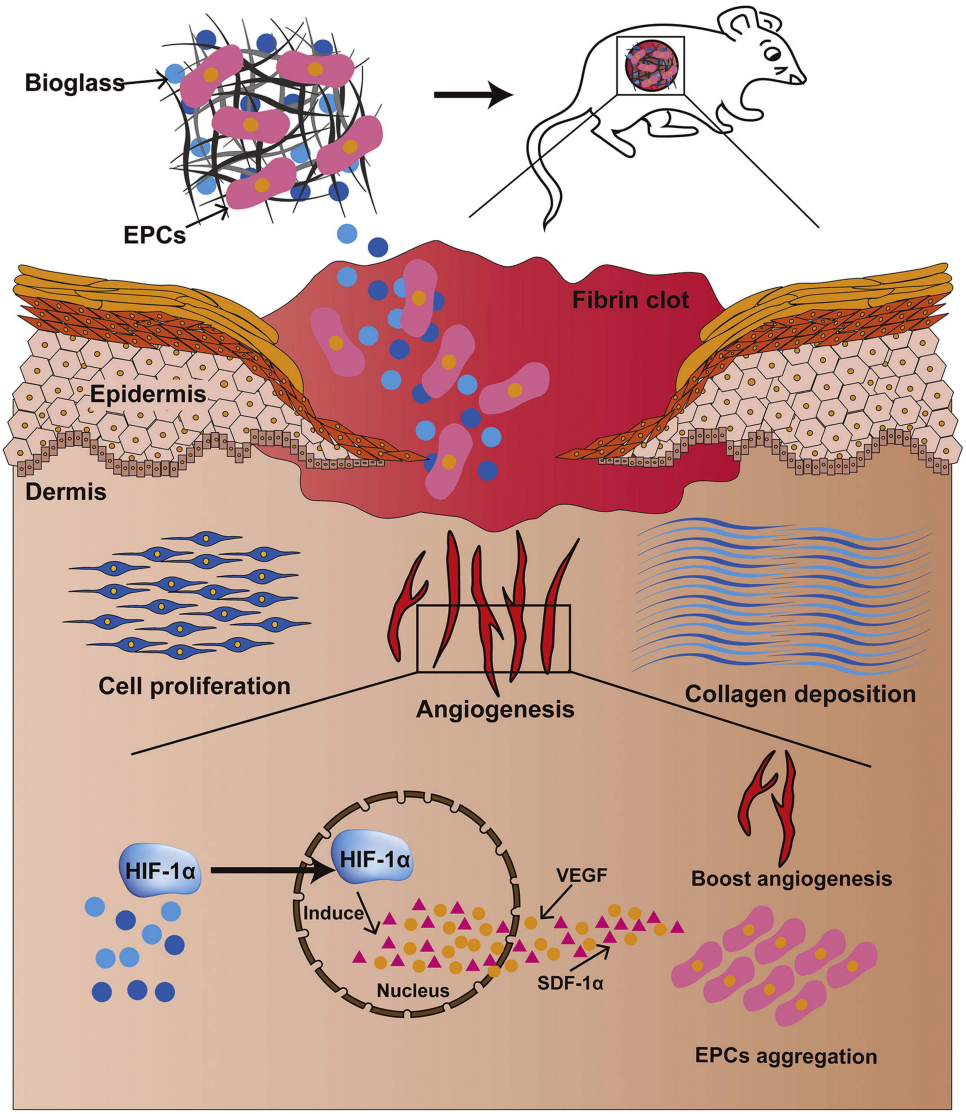

Figure 3 Schematic of a CPB/EPC construct that promotes wound healing. CPB enhances cell proliferation, collagen deposition, and EPC differentiation via the Hif-1α/VEGF/SDF-1α pathway. This results in the rapid vascularization and healing of full-thickness wounds.

Notes: Reprinted from: Wang C, Wang Q, Gao W et al. Highly efficient local delivery of endothelial progenitor cells significantly potentiates angiogenesis and full-thickness wound healing. *Acta Biomaterialia*. 2018;69:156–169. doi:10.1016/j.actbio.2018.01.019.[206] © 2018 Acta Materialia Inc. Published by Elsevier Ltd. All rights reserved. With permission from Elsevier. Available from: https://www.sciencedirect.com/science/article/abs/pii/S1742706118300308#f0060.

curcumin release and improve cell adhesion and proliferation, indicating that they could be useful in wound dressings.[207] Kaplan et al produced an injectable silk nanofiber hydrogel embedded with BMSCs. The nanofiber hydrogel maintained the stemness of the BMSCs, successfully carrying them to the target site and promoting wound healing through increased angiogenesis and collagen deposition.[57]

Usually, cell therapy in wound care is performed using micrometer-scale carriers as cell sizes fall in the range of microns. With the development of nanotechnology, an increasing number of nanofibers and NPs are being developed for cell therapy aimed at treating chronic wound given the excellent pro-differentiation, stemness-holding, and immunoregulation properties of the nanocomposites.

Collagen Modulating Systems

As an important component of the extracellular matrix, collagen mediates communication between cells, provides a scaffold for cell migration and adhesion, and plays a role in chronic wound healing.[4] Some nanobiotechnology-

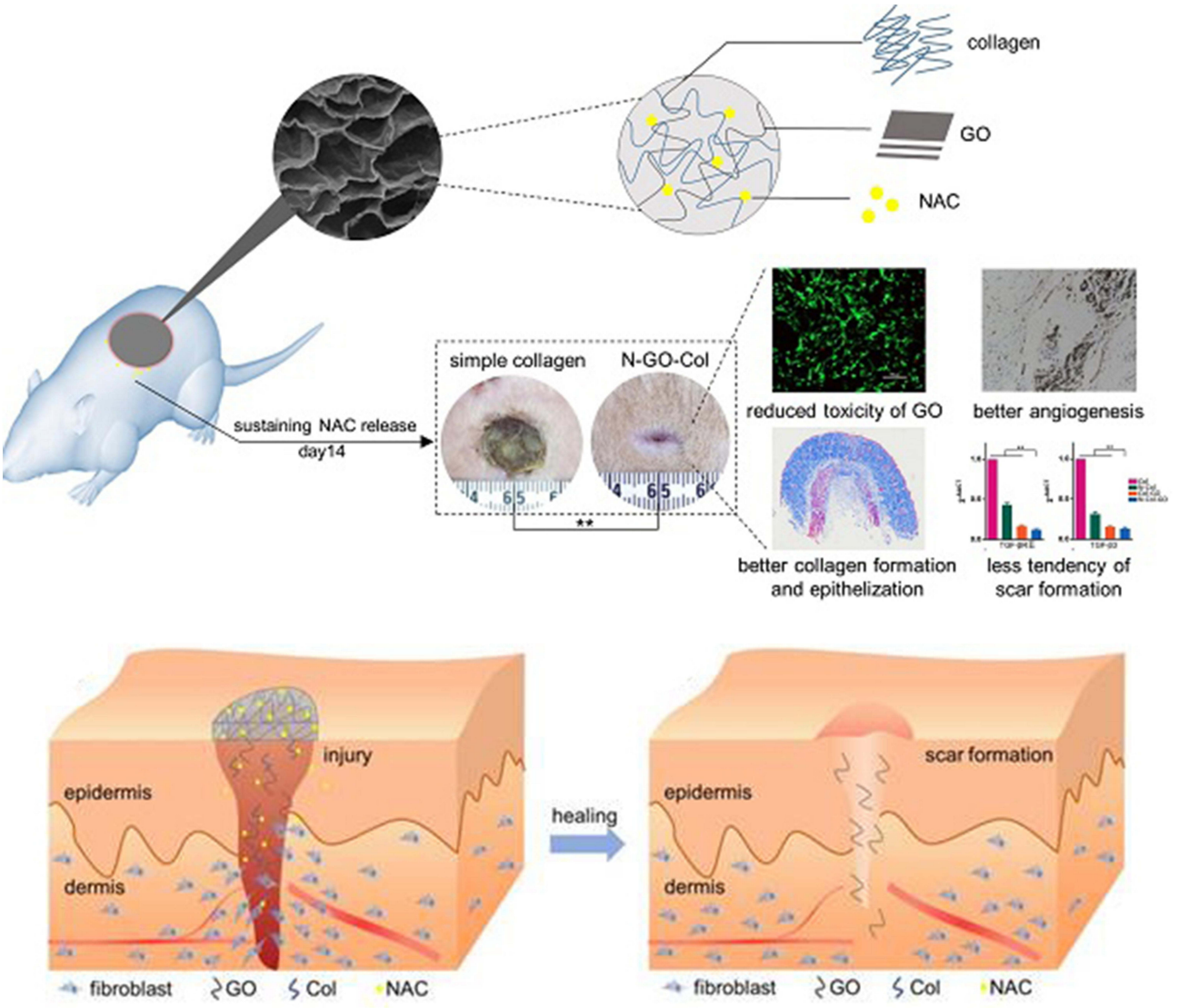

Figure 4 Wound healing effect of a scaffold based on GO NPs.
Notes: Adapted from: Li J, Zhou C, Luo C et al. N-acetyl cysteine-loaded graphene oxide-collagen hybrid membrane for scarless wound healing. *Theranostics*. 2019;9(20):-5839–5853. doi:10.7150/thno.34480.[208]

based platforms have been used for collagen modulation. Sun et al loaded N-acetyl cysteine onto graphene oxide (GO) NPs to enable scarless wound healing (Figure 4).[208] In their study, GO NPs decreased collagen metabolism and improved the balance between collagen formation and degradation, thus allowing the wound to heal without scarring. In another study by the same group, a polyamide nanofiber-based multi-layered scaffold was found to promote wound healing by encouraging the uniform arrangement of collagen.[209] Krian et al synthesized a 3-D biomatrix with nanotized praseodymium that promotes collagen function via the stabilization of native collagen. Their rare-earth metal nanoparticles thus showed potential applications in wound care.[210]

In chronic wound treatment, deposited collagen acts as a natural scaffold for cells, and therefore, modulating collagens is synonymous with re-establishing tissue structure in the wound area. As a result, collagen-modulating nano-systems have mainly been used for accelerating tissue repair. However, the studies by Sun's group are inspirational and demonstrate that this approach should also be utilized for developing chronic wound treatments that decrease scarring.

Stimuli-Responsive Systems

Despite the availability of dozens of commercial wound-care products, bionic systems have not yet been adopted for wound healing. There is an urgent need for smart wound-healing systems that can respond to the stimuli (temperature, pH, glucose, enzyme, etc.) at the site of the chronic wound area.[211,212] Through developments in nanobiotechnology, NPs with stimuli-response characteristics have received great attention. Gong et al synthesized a nanozyme consisting of poly(acrylic acid)-coated Fe_3O_4 NPs (pFe_3O_4) and then combined them with GO to produce pFe_3O_4@GO NCs. The pFe_3O_4@GO NCs could react with glucose and function as a self-supplying H_2O_2 nanogenerator at the wound site, allowing the chemodynamic treatment of wound infections.[157] Some researchers developed photoactive electrospun nanofibers using cellulose acetate, polyethylene oxide, methylene blue, and three-layered cellulose acetate/polyethylene oxide/silk fibroin/ciprofloxacin. The nanofibers could produce ROS after light irradiation at 635 nm, accelerating the healing of infectious wounds by inhibiting *S. aureus, K. pneumoniae*, and *P. aeruginosa* biofilms.[213] Zhang et al developed a hybrid hydrogel with MnO_2 nanosheets. The injectable MnO_2 nanosheet hydrogel could perform thermogenesis under 808-nm laser irradiation, eliminating ROS and inflammation and promoting wound repair.[214] Overall, nano-structures functionalized using stimuli-response properties could simulate the biological, chemical, and physical characteristics of natural skin, enabling tissue regeneration in refractory wounds.

Wound Monitoring System

Given the elucidation of mechanisms and physiological changes associated with wound healing, sensors that allow real-time monitoring of wound repair have been developed.[215–217] A complex smart wound-monitoring wound dressing has also been invented.[218] This dressing contains a nanofiber membrane made of chitosan/collagen, and promotes proliferation and regeneration by upregulating extracellular matrix secretion and promoting integrin/FAK signaling. Olivo et al added AgNPs to a fiber-based membrane monitor to increase the active surface area in the sensor, improving the detection sensitivity for biomarkers in the wound area.[219] In order to avoid secondary wound damage caused by dressing changes, Jiang et al created bacterial cellulose-based membranes with aminobenzene-boronic acid-modified gold nanoclusters (A-GNCs), which could be used for treating wounds infected with multidrug-resistant bacteria.[220] A-GNCs emit bright orange fluorescence under UV light, and the intensity of this fluorescence decreases with the release of A-GNCs. This allows healthcare professionals to determine when the dressing needs to be replaced. In the past few years, dressings that can monitor the status of chronic wounds in real-time have been tested. However, this field is relatively new, and current research on nanotech-based systems for monitoring chronic wounds is scarce.

Clinical Trials for Nanobiotechnology-Based Wound-Healing Treatments

Along with advances in nanobiotechnology research, several new nanosystems have advanced from the laboratory investigation stage to the clinical trial stage. Table 4 lists some clinical trials that have tested nano-therapies for wound healing. As early as 2014, Lopes et al investigated the cost-effectiveness of using nanocrystalline silver for treating burns. Their study showed that AgNPs provided faster wound healing than traditional silver sulfadiazine, requiring fewer dressing changes and reducing the human resource burden.[221] Meanwhile, some clinical trials tested the use of nano-products for treating chronic wounds (Table 4). Although metal NPs were typically used for antimicrobial therapy, one clinical trial studied the efficacy and safety of autologous nano-fat combined with platelet-rich fibrin for treating refractory diabetic foot wounds. However, overall, there were few clinical trials examining the applications of nanoplatforms in chronic wound care, likely owing to inadequate previous research on biocompatibility. Moreover, few doctors participated in research on nanotechnology-based chronic-wound treatment, and hence, several clinical requirements were ignored or misunderstood.

Table 4 List of Clinical Trials for Nanobiotechnology-Based Wound Treatment

Registration Date	Title	Conditions	Treatment	Type of Platform	Trial Registration Number
2014	Comparative Analysis of Cost-effectiveness of Silver Dressing in Burns (ARGENTUM)	Second-degree burn	Nanocrystalline silver	Antimicrobial system	NCT02108535
2016	Evaluation of the SPINNER Device for the Application of Wound Dressing: Treatment of Split Skin Graft Donor Sites	Skin wound	SPINNER (in situ nanofiber dressing)	Scaffold system	NCT02680106
2017	A randomized, open label, parallel-controlled trial of the efficacy and safety of autologous nano-fat combined with platelet-rich fibrin in the treatment of refractory wounds of diabetic foot	Diabetic foot wound	Nano-fat combined with platelet-rich fibrin	Delivery system	ChiCTR-INR -17013540
2018	Research on the Key Technology of Burn Wound Treatment	Burn	Nano-silver ion gel	Antimicrobial system	NCT03279549
2019	A randomized, controlled, non-inferiority study of silver sulfate gauze self-adhesive dressings for non-chronic wounds	Non-chronic wound	Nano-silver trauma patch	Antimicrobial system	ChiCTR1900024140
2019	Evaluation of Diabetic Foot Wound Healing Using Hydrogel/Nano Silver-based Dressing vs Traditional Dressing	Diabetic foot wound	Hydrogel/nano silver-based dressing	Antimicrobial system	NCT04834245

Conclusion and Future Prospects

As nanobiotechnology has developed, nano-sized biomaterials have been widely applied for treating chronic wounds. This review article highlights that the application of nanotechnology in chronic wound treatment has, so far, largely focused on scaffold construction, anti-infection treatment, and substance delivery.[34,45,47,130,147]

In scaffold systems, nanobiotechnology provides both materials and techniques for managing chronic wounds. Electrospinning, a nanotechnique, allows the production of biomimetic structures that mimic the natural skin and help in healing refractory wounds.[50] Furthermore, some nano-scaffolds promote cell adhesion and migration by mimicking the construction of natural tissues, thus promoting chronic wound healing. Nevertheless, there is further scope to improve the quality of natural nano-biomaterials and the biocompatibility of synthetic nano-biomaterials to increase their application.

Dozens of metal NPs, and especially AgNPs, have been used in antimicrobial therapy for chronic wounds.[163] However, metal deposition can cause DNA and cell damage. Hence, nanomaterials that prevent infection without causing toxicity are required. Further effort should be made to decrease the accumulation of heavy metals. Alternatively, nanocomposites without metal elements should be adopted more often in the future.

To overcome the ever-changing environment of the skin during chronic wound healing, several wound-monitoring and stimuli-responsive biomaterials have been developed.[58,157,218] By leveraging specific characteristics, such as the photothermal effect, chemo-dynamic effect, fluorescence, and thermo-sensitivity, more nano-biomaterials that can be used in stimuli-responsive and dynamic monitoring systems for wound care should be developed. Most studies on wound healing have focused on migration-promoting effects, antimicrobial activity, and substance delivery. However, few nanotech-based multifunctional smart systems, such as smart dressings that show specific responses to stimuli, have

been developed. Researchers in this field should work towards developing smart systems based on the mechanisms of disunion in chronic wounds, which could effectively demonstrate the potential of nanobiotechnology in promoting chronic wound repair.

Despite the decades-long history of nanotechnology research, few products and therapies based on nanobiotechnology have become available commercially or entered the clinical trial phase. One reason for this is that most basic nanotech research on chronic wound healing is performed in rodent models, such as C57BL/6 mice or Sprague–Dawley rats, even though the skin structure and chronic wound healing processes differ between rodents and humans.[222] The wound healing effects observed in primates, such as humans, may not be as good as those in rats and mice. Meanwhile, the cost of nano-materials and processing platforms required for large-scale preparation also hinder the clinical translation of nanotechnologies.

During the past few years, numerous nano-materials and techniques have been used to repair chronic wounds. This review summarizes some nanobiotechnology-based systems and nanoplatform designs that can be used for treating chronic wounds. It highlights that a smart dressing for chronic wounds that allows real-time monitoring and has stimuli-responsive abilities is one possible direction for the future of nano-wound-repairing systems. We hope this review motivates the development of more sophisticated wound management systems based on nanobiotechnology in the future.

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Disclosure

The authors report no conflicts of interest in relation to this work.

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