

Nanomedicine in Chronic Wound Management: Current Challenges and Future Directions

Ms . Damini A. Patil, Mr. Vaibhav V . Patil . Mr. Harshal P. marathe
Smt. Sharadchandrika Suresh Patil College of Pharmacy, Chopda.

Abstract: Chronic wounds indeed present a high mortality risk, accompanied by annoying costs' which is a literal paraphrase to the general belief that poor healing chronic wounds are common around the world which in turn also is common around the globe. If one delves into the three problems areas concerning chronic wounds – Lack of the appropriate conditions to trigger the processes of cell migration, proliferation and formation of new blood vessels, affliction due to bacterial infection, along with persistent and overactive inflammation. There is no doubt that current clinical methods of Chronic Wound Treatment Are Associated with Major Pitfalls. Barring a miracle, prospects for clinical deployment appear dismal. It is evident that over the past decade the science of nanomedicine had definitely assisted in dramatically changing the paradigm. Some of these things may be too good to be true. Those things include some of the claims proposed by authors on the effects of nanomedicine. These specifics target a variety of things. This review specifically features three areas: First – it discusses mechanisms and characteristics of the process concerning wounds. Second – this review intends to present not only the topical research but also research considering paediatric CWD.'

Keywords: Nanomedicine; wound healing; scaffold; nanocarriers; nanoparticles; innovative strategies; Dressings infectious control etc.

INTRODUCTION

Inflammation, proliferation, remodeling, and hemostasis are the four sequential but overlapping biological steps that make up the highly coordinated process of wound healing. 1 – 4

A chronic wound status may result from any disruption of any of the aforementioned wound-healing phases, caused by both internal and external sources. This could prolong each step and result in an unsatisfactory outcome. When it comes to full wound healing, the most common problem is the colonization of contaminating bacteria at the site of skin damage during the natural healing process. 4.

A chronic wound Is one that, in addition to

unresolved inflammation and the presence of infection, is unable to heal and regain anatomical and functional integrity because of significant impairment of the healing processes of angiogenesis, epithelial migration, and cell proliferation. 5 – 8 With 5-year mortality rates of almost 50% and a prevalence of 1% to 2% of the general population, same to heart failure rates, chronic wounds are rapidly being recognized as a serious, life-threatening illness that has significant financial consequences. 8

Clinical success in healing chronic wounds has been limited despite significant efforts to develop strategies and market various therapeutic products. This is primarily due to the complexity of the healing process and our incomplete knowledge of the biological, biochemical, immunological, and mechanical repair processes involved in skin regeneration. 8 -13 Our current approach to treating chronic wounds includes wound management techniques like debridement, the use of different dressing types including hydrocolloid, hydrogels, and foams, as well as mitigating the factors that lead to wounds such using off-loading devices or negative pressure wound therapy. Advanced treatments include growth hormones, bioengineered skin substitutes, and eventually autologous skin grafts are also required for more serious wounds. 14 – 15

Many commercially available products, such as Integra, Apligraf, Purilon, and Nu-gel, have been created to hasten the healing of chronic wounds. The outcomes of treating chronic wounds remain below ideal despite all of these treatments. Problems like bleeding, discomfort, or infections are linked to wound debridement. The catabolic wound environment and the presence of biofilms impede the topical administration of medicines like growth hormones or antibiotics. 16

The limitations of the current wound dressings,

which include poor mechanical qualities and frailty in terms of adhesion, extensibility, and elasticity, make them subpar. Due to these deficiencies, secondary dressings must be applied, which further complicates the healing process by raising the possibility of infection or excessive damage.¹⁷⁻¹⁹ Furthermore, most current products only target one of several compromised systems, which significantly hinders their ability to promote the healing of chronic wounds. ¹⁷⁻¹⁹

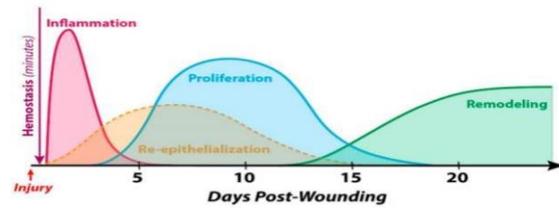
Nanomedicine approaches have introduced advances in the diagnosis and treatment of various diseases including diabetes, cardiovascular disease, tissue trauma, tissue engineering, regenerative medicine, inflammatory diseases, and wound healing. ²⁰⁻²⁵

Nanotherapeutics, including the use of nanoparticles and nanofibers, can overcome the refractory chronic wound in multiple manners (Table 1). Nanoparticles as carrier materials can improve the efficiency of wound healing pharmaceuticals such as antibiotics, growth factors, or anti-inflammatory agents by enhancing their bioavailability via increasing their solubility, increasing their half-life, improving their stability, and preventing their degradation and minimizing their potential toxicity.²⁶⁻²⁷

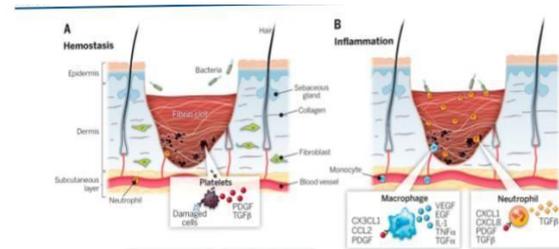
In this review, we focus on the physiological mechanisms and pathology of normal and chronic wounds. We also discuss the role of nanomedicine in addressing the main issues associated with chronic wounds, offering a brief discussion of the challenges.

PHYSIOLOGY OF WOUND HEALING

The skin has the largest surface area of any organ in the human body, which should come as no surprise. It offers a vital anatomical barrier that shields different interior tissues from infections, heat, and mechanical harm. Because of this, the skin is extremely susceptible to several kinds of damage, which significantly affects patients as well as the healthcare system's financial situation. The delicate synchronization of several cell types, chemokines, cytokines, and growth factors in successive phases is necessary for the complex physiological process of skin restoration. Hemostasis, inflammation, proliferation, and remodeling are the four consecutive and overlapping processes that traditionally define the wound healing cascade. ²⁸⁻³⁰



Hemostasis, which reduces bleeding after vascular damage and stops bleeding altogether, is the initial reaction to injury at the wound site. The three stages of hemostasis—vasoconstriction, primary hemostasis, and secondary hemostasis—are accomplished by quick, simultaneous, and mechanistically linked pathways. Blood flow to the wounded area is slowed while the clot forms due to vasoconstriction, which is caused by the transient reflexive contraction of vascular smooth muscles.³¹ Reducing the rate at which blood reaches the wounded area while the clot develops. Endothelin, which is secreted from injured endothelium, is one of the several vasoconstrictors that cause vasoconstriction. However, it only stops bleeding temporarily because hypoxia and wound-related acidosis cause passive muscular relaxation, which permits bleeding to continue.³²



Inflammation

After an accident, inflammation occurs right away and can persist for up to three days. Platelet degranulation starts a complement cascade and the synthesis of strong complement peptides after the severe vasoconstriction of early hemostasis. These peptides encourage the release of histamine, serotonin, proteases, and other cellular mediators from mast cells and basophils. This causes vasodilation, which raises blood flow and vascular permeability and gives the appearance of heat and redness. Fluid buildup and swelling are caused by the release of fibrinogen and other plasma-derived substances that act as chemoattractants for the infiltration of inflammatory cells like neutrophils into the wound due to vasodilation and increased blood vessel permeability.³³

The first circulating inflammatory cells to reach the

wound site are neutrophils. Their main function is phagocytosis, which is the ingestion and elimination of dead cells, damaged matrix elements, bacteria, and other foreign particles. By releasing toxic granules, neutrophils further combat infectious threats by creating neutrophil extracellular traps in addition to an oxidative burst. Numerous chemical signaling mechanisms, such as the complement cascade, interleukin activation, and transforming growth factor- β (TGF- β) signaling, control this process and enable neutrophils to migrate into the wound along a chemical gradient—a process known as chemotaxis.³⁴ The leukocyte recruitment cascade, which includes rolling, adhesion, crawling, and migration to the inflammatory tissue, is started when neutrophils attach to the endothelium through adhesion receptors such as selectins/selectin ligands and integrins. This process attracts other neutrophils to the location. Monocytes and other mononuclear cells are quickly drawn from the spleen or bone marrow two days following an injury, when they frequently undergo differentiation into different kinds of dendritic cells and tissue macrophages.³⁴

Proliferation phase

The proliferation phase, which begins 4 days after wound development and lasts 21 days in serious wounds, involves tissue granulation, wound contraction, and angiogenesis. It is triggered by platelet production of TGF- β , PDGF, and FGF, which induces neovascularization and repair of blood vessels. Fibroblasts accumulate in the wound site.³⁵

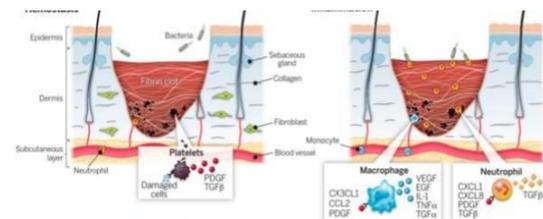
Fibroblasts accumulate in wounds and lay down extracellular matrix proteins, generating collagen and fibronectin. Granulation tissue, developed during inflammation, replaces clots and aids in re-epithelialization. Inflammatory cytokines stimulate fibroblasts to release growth factors, allowing keratinocytes to migrate to the wound bed. Granulation tissue hosts cellular-ECM interactions and releases biomolecules, facilitating fibroblast differentiation into myofibroblasts, which draw wound margins together.²⁶

The Remolding phase

The last step of wound healing is The maturing or remodeling phase. This stage begins around Week 3 postwounding and may take one year or longer, Depending on the wound type, and results in the growth of Natural epithelium and maturation of scar

tissue.³⁶

The type III collagen (reticular collagen) laid down during the proliferation phase is gradually replaced by the more-stable type I collagen. Fibroblasts then remodel their surroundings by degrading and depositing new collagen, which with further collagen cross-linking results in the realignment of collagen into organized networks that increase the tissue's tensile strength, reaching maximum of 80% that of unwounded skin.³⁷ Wound repair is a complex process involving a sequence of phases, and failure to follow or maintain optimal synchrony can lead to chronic wounds.



C. proliferation D The Remolding phase

Nanomedicines strategies to address bacterial infection :-

Chronic wounds are often infected. While the host defence system initially controls the growth and spreading of microorganisms, pathogens such as bacteria can rapidly evolve, adapt, or develop biofilms; the resulting microbial infection can Impair wound healing. nanomedicine has already demonstrated a promising capacity to eliminate infections⁽³⁸⁻⁴⁰⁾ . nanomaterials are currently being used as direct antimicrobial agents, due not only to their “nano” features but also their intrinsic antimicrobial effect, and as carriers of antibiotics or other antimicrobial agents ⁽⁴²⁻⁴⁵⁾

The physical Interaction between NPs and cell walls of bacteria is mediated by van der Waals, Hydrophobic, or electrostatic forces and/or receptor–ligand Interactions that affect the permeability and/or integrity of the Membrane. NPs can also cross the cell membrane and Adversely interact with various subcellular components Including proteins and DNA. The NP-induced oxidative/ Nitrosativstress, protein deactivation, and up/down regulation entiation of cells, killing multidrug-resistant bacteria, and Preventing biofilm formation. The code livery of LL37 and serpin A1 improved wound healing by suppressing inflammation in BJ fibroblast cells and keratinocytes,

increasing collagen-I deposition, and enhancing antibacterial effects against both Gram-positive (*S. aureus*) and Gram-negative (*E. coli*) bacteria. (46)

In similar study, the LL37NPs with photodynamic properties are a new generation of antibacterial agents capable of killing bacteria through generating ROS (47-49).

Which they do only under irradiation, Making it possible to control ROS production and minimize its Side effects. Simultaneous bacterial eradication and tissue Regeneration are effective in preventing the impairment of Normal tissues around the wound. Light-responsive multifunctional NPs were developed for simultaneous production of ROS and sustained release of magnesium ions, which is Necessary for the activation of crucial enzymes and proteins, Cell differentiation, and tissue regeneration. The multifunctional NPs were synthesized by conjugation of quaternary Ammonium chitosan and photosensitizer chlorin e6 (Ce6), and Then a Mg/(-)-epigallocatechin-3-gallate (EGCG) complex Was encapsulated into the NPs. At 660 nm laser irradiation, This NP produced ROS, eradicated both *E. coli* and *S. aureus*, And quickly reduced inflammation. It also released magnesium Ions, promoting the proliferation and migration of endothelial Cells and wound healing. The multifunctional NPs consisting of Photodynamic and chemical agents simultaneously improved Wound healing and destroyed bacteria without adverse Effects (50).

Thanks to its photodynamic properties (the surface plasmon Resonance effect), Ag/AgBr-loaded mesoporous silica NPs (Ag/AgBr/MSNs) killed *S. aureus* and *E. coli* after 15 min of Light irradiation by producing ROS and inducing oxidative Stress in critical biomolecules. Ag/AgBr/MSNs also released Ag⁺ ions that not only damaged bacteria but also activated an Immune response, eliminating the infection. Therefore, Ag/ AgBr/MSNs are promising candidates for simultaneous Disinfection and enhancement of healing in wounds. (51)

Injectable in situ forming hydrogels with antibacterial Properties have proven to be effective wound- dressing agents. Methicillin-resistant *Staphylococcus aureus* (MRSA) infection is A challenging issue that can be addressed through the. Development of wound dressing hydrogels. (52)

Silver NPs Decorated with reduced graphene oxide

were incorporated into A poly(N-isopropylacrylamide166-co-nbutylacrylate9)-poly (ethyleneglycol)-poly(N-isopropylacrylamide166-co-n- butyl Acrylate9) (PEP) copolymer scaffold to produce a thermosensitive hydrogel with antibacterial properties. The sol-gel Transition temperature, LCST (lower critical solution temperature), was adjusted to be below body temperature by Copolymerization N-isopropyl acrylamide with polyethylene Glycol and a small amount of a hydrophobic monomer, Hydrophobic n-butyl acrylate. Interestingly, the incorporation Of Ag@rGO Nano sheets into the micelle network of the PEP Hydrogel, resulted in the formation of a reinforced and Physically cross-linked inorganic/polymeric dual network, thus Inducing the irreversibility in the cooling cycle. This skin Temperature-responsive hydrogel was then sprayed on the skin, And its stability on human hand skin at warm temperatures (indoors) and cold temperatures in the winter (outdoor) was demonstrated. This hydrogel was shown to rapidly destroy MRSA and enhance the healing of sharp and deep MRS infected wounds (within 2 weeks of the study time).(53)

In a similar study, tebiium ions (Tb3+) and reduced graphene Oxide were incorporated into a poly(vinyl alcohol) hm (PVA)- Alginate (SA) hydrogel to treat biofilm-infected diabetic Wounds. Once a biofilm forms, wound healing is complicated And delayed, since the biofilm impedes the access of Therapeutics, including immune cells and drugs used for Disinfection, to the bacteria buried underneath.(54)

Therefore biofilm-disrupting Nano composites were developed. Rare earth Elements such as Tb3+ attach to peptidoglycan and destroy the Bacterial membrane. Although they are relatively stable, they Do not induce bacterial resistance. A combination of reduced Graphene oxide and Tb3+ showed synergistic bactericidal Effects and disrupted the biofilm of both Gram-negative (*Aeruginosa*) and Gram-positive (*S. aureus*) bacteria and Promoted diabetic wound healing. (55)

A hydrogel Nano fibrous membrane composed of a photoactive polymer NP-in-classical polymer nanofiber robustly Killed Gram-negative (*E. coli* K-12) and Gram-positive (*Bacillus Subtilis*) bacteria and prevented biofilm growth when exposed To visible light. The disinfecting ability of these light-responsive Nano fibrous membranes is based on their capability of Producing active oxygen species

(102) under light irradiation.(56)

Photo thermal therapy under NIR irradiation is a non-invasive And convenient approach to kill bacteria through localized Hyperthermia.(57)

A hybrid hydrogel consisting of 3-(trimethoxysilyl)propyl methacrylate and mesoporous silica modified CuS NPs showed photo thermal and photodynamic Properties. Under NIR irradiation, it increased in temperature, Induced oxidative stress, and released ROS (such as hydroxyl Radicals) that denatured structural proteins and disrupted the Bacterial membrane (both *S. aureus* and *E. coli*). In addition, This hybrid hydrogel released copper ions that not only Degraded bacterial DNA and proteins but also triggered cell Proliferation, angiogenesis, and tissue regeneration at the Wound site (Figure 5)(58)

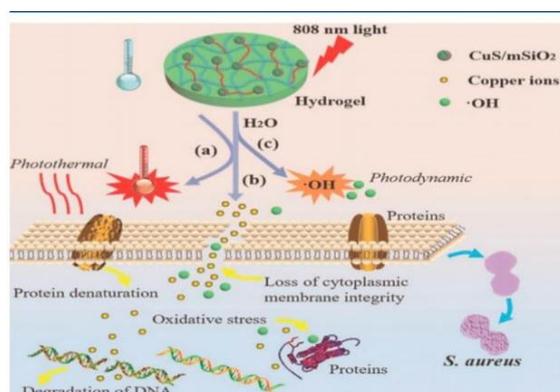


Photo thermal therapy is a controllable localized heating/ Killing of bacteria under irradiation. It is very unlikely to induce Drug resistance and does not have systemic effects. However, High irradiation/local temperature is required for the Eradication of all bacteria in the wound, which may damage The adjacent area. Therefore, photo thermal therapy is usually considered a supportive approach rather than the main goal in the development of multifunctional NPs. MoS₂ Nano sheets Modified with polydopamine (PDA) and silver eradicated *S. Aureus* biofilms and accelerated infected wound healing. Photo thermal therapy weakens or destroys the protective Structures of biofilms and bacteria, making them leakier to Silver ions. Therefore, photo thermal therapy increases the Bactericidal effects of silver ions in a synergic manner. (59)

Therefore, the formulation of antibacterial, Pro-angiogenic, and other wound-regenerative Nano therapeutic Agents may solve the conundrum of intervening in the complex Orchestration of the wound healing process. While the discussed NPs

have antibacterial properties, the Contradictory reports on their biocompatibility may inhibit Their clinical translation.(60-61) .

Since numerous parameters Including size, charge, composition, and shape of nanomaterials can affect their toxicity, part of the discrepancy in results May be attributed to a lack of full characterization or other Ignored factors influencing the cytotoxicity of NPS (62-63)

Still, The potential toxicity of NPs, especially metallic or metal oxides NPs, can be an alarming factor, limiting the usefulness of Antibacterial NPs. In fact, silver-containing dressings are not. Generally recommended to be used for the long-term. (64)

Generally recommended to be used for the long-term(65). Several studies have shown that the release of Ag⁺ ions from Sliver NPs especially above the toxic threshold concentration Can be toxic to cell lines, damaging DNA and breaking the DNA strand.(66-68)

Interference with DNA repair pathways or Damage to mitochondria can also induce toxicity in cell lines Exposed to silver nanoparticles. Besides, NP properties such as Shape have been shown to influence the toxicity, and therefore, Care should be paid when using the silver NPs for biomedical Applications. For example, Holmes et al. showed that Ag NPs With different shapes and crystallographic structures have a Different cytotoxicity effect on both bacteria and keratinocytes Cells with the truncated plate-shaped Ag NPs, resulting in the Highest cytotoxicity.(69) .

Moreover, in addition to the intrinsic Toxicity, residual impurities may also contribute to the toxicity Response of NPs. For example, the toxicity study of Ag NPs With various sizes, ranging from 20 to 80 nm, purity state (washed or unwashed), and carbon-coated against primary Human keratinocytes, indicated that the main cause of toxicity Is the residual contaminants, formaldehyde rather than the particle itself. (70) .

Among all of the NPs discussed here, silver NPs are the only Nanomaterials that have been used commercially in wound Dressing products. Nanocrystal silver used in wound dressing Such as Anti coat is produced by physical vapour deposition, Which yields nanocrystals deposition on the surface with about 15 nm across, which is between 30 and

50 atoms.(71)

These Products are reported to be nontoxic compared to silver Sulfadiazine or silver nitrate containing products, since silver Nanocrystals are designed to dissolve slowly and release the Silver ion (with a maximum concentration of 70 ppm) that is Still within the toxic range for keratinocytes and fibroblasts. (72-73)

Nano medicine strategies to improve angiogenesis

During angiogenesis, new blood vessels grow from the existing Vasculature to allow the delivery of oxygen and nutrients as Well as components of the inflammatory response during Wound healing. Angiogenesis occurs throughout life in both Health and disease and plays a key role in the pathophysiology Of different disease processes such as tumour promotion, Metastasis, retinopathy, and coronary artery disease. Angiogenesis is a normal and vital component of the proliferative Phase of wound healing, during which new capillaries grow Into a wound space after injury and form granulation tissue. Without angiogenesis, skin healing would be limited to the Most superficial wounds. While acute wound healing produces Normal granulation tissue, impaired angiogenesis in chronic Wounds results in defective granulation tissue, delaying Progression to the proliferation phase. Angiogenesis is deficient In virtually all chronic wounds such as diabetic foot ulcers, Venous insufficiency ulcers, and ischemic ulcers. (74) .

Alternatively, simulation of the Nano topographic features of primary blood vessel cells as well as the Delivery of chemical signals by nanomaterials can also stimulate Angiogenic effects, facilitating the creation of new blood vessels In chronic wounds, which suffer from reduced vascularity and Blood flow. Nanomaterials, in general, can stimulate angiogenesis by promoting endothelial cell migration, activating Redox signalling, regulating cytoskeleton rearrangement, or by Forming focal adhesions.(75).

ROS formation has also been Shown to be involved in redox signalling pathways during Angiogenesis. (76).

Various nanomaterials have been reported to promote Angiogenesis in tissue regeneration scenarios such as bone Repair, nerve tissue repair, repair after ischemia reperfusion, And wound healing. (77).

In fact, the use of nanomaterials to Promote angiogenesis may become a welcoming alternative to The traditional use of growth factors such as VEGF-A or PDGF, Which may promote pathological angiogenesis, thrombosis, And fibrosis.(78)

Nano medicine strategies to improve chronic Inflammation-:

Nano devices are a promising approach to manage inflammation and aid healing in chronic wounds. Au NPs were used to deliver carbon monoxide-releasing molecules into bovine serum albumin (BSA), which have low water solubility and rapid release of CO. Gold NPs were used to extend their circulatory half-life and improve targeted delivery and sustained release of loaded CO.79-80

Persistent inflammation, leading to overexpression of inflammatory factors and generation of extra reactive oxygen species (ROS/RNS), is another challenge to wound healing. Chitosan-coated CeO₂ nanotubes (CCNs) enhanced wound healing by preventing persistent inflammation. CCNs accelerated wound healing by reducing the expression of inflammatory cytokines (TNF- α) and increasing the expression of anti-inflammatory and antioxidant enzymes. Fullerenes and carbon nanotubes are powerful antioxidants with a strong capacity to scavenge and detoxify ROS.81-83

NP systems can be beneficial in all stages of wound healing, such as accelerating haemostasis through a Nano bridging effect, adsorbing onto polymers or protein chains, and eradicating bacterial infections. They can also capture excess ROS and release their loaded arginine under the catalysis of inducible NO synthase (iNOS), producing nitric oxide (NO), which in combination with L-arginine can promote the proliferation stage of wound healing.84

Persistent inflammation in diabetic wounds can hinder wound healing after surgery. Anti-inflammatory drugs can be cleared through oral or intravenous administration. Nano porous nanoparticles (NPs) coated with mannose can deliver the loaded drug to activated macrophages, reducing inflammation and promoting wound healing. Curcumin-loaded chitosan can enhance wound healing by inhibiting macrophage-mediated inflammation and disinfecting the wound area. MicroRNAs, like MiR-146a, can regulate gene expression and suppress inflammatory factors at the

RNA level. NP-mediated delivery of MiR-146a could be a promising approach to suppress inflammatory factors in diabetic patients. Mesoporous silica nanoparticles (MSNs) can restore tissue integrity without suturing due to their ability to adsorb on tissue fibres and act as connectors.⁸⁵⁻⁸⁶

NANOMEDICINE STRATEGIES FOR IMPROVING SCAFFOLDING:-

Many topological formulations have been used in studies of chronic skin wound healing, including hydrogel dressings, membranes, or sponges made from collagen, hyaluronic acid, or other biopolymers. However, these topological formulations do not represent the innate architecture of skin ECM and lack the ability to recapitulate it. Chronic wounds with an inadequate mass of dermal appendages may require engineered dressings that mimic the skin's architecture and stimulate cell migration into the defect site.⁸⁷⁻⁸⁸

Moisture became a key parameter in the design and development of wound dressings, which are classified as passive, interactive, advanced, or bioactive. Passive meshes simply support wound healing by covering the wound, interactive meshes create a moist wound environment and facilitate the flow of moisture and gas, while offering protection from trauma and pathogens. Advanced dressings provide and sustain a moist wound environment and promote the healing process.⁸⁹

Nanoparticle-filled designing materials have shown promising potential for wound healing. Nano fibrous dressings containing nanoparticles have shown promising potential due to their large surface area, interconnected porosity, and ECM-like architecture. Studies have shown that nanofibers, used as granulation tissue substitute, improve endothelial angiogenic potential and neovascularization in diabetic wound healing models.⁹⁰⁻⁹²

Various techniques for fabricating Nano fibrous meshes have been reported, such as electrospinning, which has been used in the production of fibrous membranes for the treatment of chronic wounds. Electro spun hyaluronic acid (HA) has been shown to have numerous advantages for the treatment of full-thickness wounds in pig models compared to common dressings such as solid HA film, adhesive bandage, gauze with petroleum jelly (Vaseline), and antibiotic dressing.⁹³

Future accepts& challenges:-

Chronic wound treatment remains a challenge due to infection, inflammation, and lack of proper angiogenesis. Despite advances in wound dressings, many are mono functional and designed to maintain moisture, control bacterial overburden, or promote cell migration. A multifunctional dressing is needed to address infection, inflammation, and angiogenesis simultaneously. This dressing should combine a suitable physical mechanical environment with multiple therapeutic biomolecules to accelerate healing, identify infection and healing indicators, release drugs or bioactive molecules, minimize microbial biofilm formation, and have essential extracellular components like collagen and elastin.

Nanotechnology has the potential to design multipurpose dressings and shed light on the pathophysiology of chronic wounds at the molecular level. Nano probes could detect factors in wounds, such as pH, ROS, inflammatory cytokines and enzymes, or identify changes in inflammatory status. However, no dressing is currently capable of detecting specific proteins in the wound. Nanomedicine could play a pivotal role in designing smart delivery systems for controlled release of anti-inflammatory and angiogenic factors into wounds, protecting them against harsh conditions, degrading enzymes, or extreme pH, and stimulating fibroblast and keratinocyte proliferation.⁹⁴⁻⁹⁵

However, there is still a long way to go before we can fully leverage nanotechnology in treating chronic wounds. The application of nanotechnology in commercial wound dressings is mainly limited to antibacterial wound dressings containing silver nanocrystals. The majority of approved nanoparticles for nanomedicine are designed for cancer treatment, and very few inorganic nanoparticles are currently approved for clinical use or in clinical trials.^{96,97}

One main challenge is the lack of necessary and accurate data on the fate and toxicity of nanomaterials (NPs), due partly to the complex nature of NPs and the challenges inherent to their characterization. Factors such as the formation of bio molecular corona on NPs designed for chronic wound applications need to be studied in detail before proceeding to clinics.⁹⁸

CONCLUSION

In conclusion, the exploration of nanotechnology in chronic wound care provides landscape rich with opportunities, challenges, and potential innovations. The introduction highlighted the important need for advanced therapeutic strategies in managing chronic wounds, setting the stage for the subsequent exploration. The examination of various nanoparticle types elucidated their mechanisms in wound healing, exhibits the resources fullness of lipid-based, polymeric, and inorganic nanoparticles. Real-world efficacy was demonstrated through case studies and clinical trials, affirming nanotechnology's success in promoting wound healing. opportunities in nanomedicine for chronic wounds, particularly targeted drug delivery and enhanced cellular uptake, emerged as key avenues for precision interventions. However, challenges, including biocompatibility concerns and regulatory hurdles, were acknowledged, emphasizing the importance of rigorous evaluation and streamlined regulatory pathways. Looking to the future, advancing nanotechnologies and potential breakthroughs, such as nano engineered scaffolds and the integration with AI, offered glimpses into a dynamic landscape where personalized approaches and innovative technologies converge to redefine chronic wound management. This comprehensive review underscores the crucial role of nanotechnology in renewing chronic wound care. By understanding mechanisms, applications, challenges, and future possibilities, the work lays the foundation for a new era in precision wound management.

Collaboration between interdisciplinary teams is paramount as we navigate the complexities, ensuring responsible and effective integration of nanotechnology into routine clinical practice. This exploration serves as a roadmap for researchers, clinicians, and policymakers alike, guiding the ongoing efforts to harness the full potential of nanotechnology in addressing the persistent challenges posed by chronic wounds.

REFERENCES

- [1] Guo, S.; DiPietro, L.A. Factors affecting wound healing. *J. Dent. Res.* 2010, 89, 219–229. [CrossRef]
- [2] Eming, S.A.; Martin, P.; Canic, M.T. Wound repair and regeneration: Mechanisms, signaling, and translation. *Sci. Transl. Med.* 2014, 6, 265sr6. [CrossRef] [PubMed]
- [3] Gurtner, G.C.; Werner, S.; Barrandon, Y.; Longaker, M.T. Wound repair and regeneration. *Nature* 2008, 453, 314–321. [CrossRef] [PubMed]
- [4] Edwards, R.; Harding, K. Bacteria and wound healing. *Curr. Opin. Infect. Dis.* 2004, 17, 91–96. [CrossRef] [PubMed]
- [5] Eming, S. A.; Martin, P.; Tomic-Canic, M. Wound repair and regeneration: mechanisms, signaling, and translation. *Sci. Transl. Med.* 2014, 6 (265), 265sr6–265sr6.
- [6] Armstrong, D. G.; Wrobel, J.; Robbins, J. M. Guest Editorial: are diabetes-related wounds and amputations worse than cancer?
- [7] *International wound journal* 2007, 4(4), 286–287. (6) Aulivola, B.; Hile, C. N.; Hamdan, A. D.; Sheahan, M. G.; Veraldi, J. R.; Skillman, J. J.; Campbell, D. R.; Scovell, S. D.; LoGerfo, F. W.; Pomposelli, F. B., Jr Major lower extremity amputation: outcome of a modern series. *Arch. Surg.* 2004, 139 (4), 395–399.
- [8] Nussbaum, S. R.; Carter, M. J.; Fife, C. E.; DaVanzo, J.; Haught, R.; Nusgart, M.; Cartwright, D. An Economic Evaluation of the Impact, Cost, and Medicare Policy Implications of Chronic Nonhealing Wounds. *Value Health* 2018, 21 (1), 27–32.
- [9] Ovington, L. G. Advances in wound dressings. *Clinics in Dermatology* 2007, 25 (1), 33–38.
- [10] Falanga, V.; Sabolinski, M. A bilayered living skin construct (APLIGRAF®) accelerates complete closure of hard-to-heal venous ulcers. *Wound Repair and Regeneration* 1999, 7 (4), 201–207.
- [11] Ikada, Y. Challenges in tissue engineering. *J. R. Soc., Interface* 2006, 3 (10), 589–601.
- [12] Gurtner, G. C.; Werner, S.; Barrandon, Y.; Longaker, M. T. Wound repair and regeneration. *Nature* 2008, 453 (7193), 314.
- [13] Bello, Y. M.; Falabella, A. F.; Eaglstein, W. H. Tissue-Engineered skin. *American journal of clinical dermatology* 2001, 2 (5), 305–313
- [14] Han, G.; Ceilley, R. Chronic Wound Healing: A Review of Current Management and Treatments. *Adv. Ther.* 2017, 34 (3), 599–610
- [15] Shi, C.; Wang, C.; Liu, H.; Li, Q.; Li, R.; Zhang, Y.; Liu, Y.; Shao, Y.; Wang, J. Selection of Appropriate Wound Dressing for Various Wounds. *Front. Bioeng. Biotechnol.* 2020, 8, 182–182.
- [16] Barrientos, S.; Stojadinovic, O.; Golinko, M. S.; Brem, H.; Tomic-Canic, M. PERSPECTIVE

- ARTICLE: Growth factors and Cytokines in wound healing. *Wound Repair and Regeneration* 2008, 16 (5), 585–601.
- [17] Zhong, S.; Zhang, Y.; Lim, C. Tissue scaffolds for skin wound Healing and dermal reconstruction. *Wiley Interdiscip. Rev.: Nanomed. Nanobiotechnol.* 2010, 2 (5), 510–525.
- [18] Dreifke, M. B.; Jayasuriya, A. A.; Jayasuriya, A. C. Current Wound healing procedures and potential care. *Mater. Sci. Eng., C* 2015, 48, 651–662.
- [19] Jayakumar, R.; Prabakaran, M.; Kumar, P. S.; Nair, S.; Tamura, H. Biomaterials based on chitin and chitosan in wound dressing Applications. *Biotechnol. Adv.* 2011, 29 (3), 322–337.
- [20] DiSanto, R. M.; Subramanian, V.; Gu, Z. Recent advances in Nanotechnology for diabetes treatment. *Wiley Interdiscip Rev. Nanomed Nanobiotechnol* 2015, 7 (4), 548–64.
- [21] Chandarana, M.; Curtis, A.; Hoskins, C. The use of Nanotechnology in cardiovascular disease. *Appl. Nanosci.* 2018, 8(7), 1607–1619.
- [22] Bharadwaj, V. N.; Nguyen, D. T.; Kodibagkar, V. D.; Stabenfeldt, S. E. Nanoparticle-Based Therapeutics for Brain Injury. *Adv. Healthcare Mater.* 2018, 7 (1), 1700668.
- [23] Danie Kingsley, J.; Ranjan, S.; Dasgupta, N.; Saha, P. Nanotechnology for tissue engineering: Need, techniques and Applications. *J. Pharm. Res.* 2013, 7 (2), 200–204.
- [24] Yang, Y.; Chawla, A.; Zhang, J.; Esa, A.; Jang, H. L.; Khademhosseini, A. Applications of Nanotechnology for Regenerative Medicine; 580 -584
- [25] Rajendran, N. K.; Kumar, S. S. D.; Houreld, N. N.; Abrahamse, H. A review on nanoparticle based treatment for wound healing. *J. Drug Delivery Sci. Technol.* 2018, 44, 421–430.
- [26] Parani, M.; Lokhande, G.; Singh, A.; Gaharwar, A. K. Engineered Nanomaterials for Infection Control and Healing Acute And Chronic Wounds. *ACS Appl. Mater. Interfaces* 2016, 8 (16), 10049–10069.
- [27] Rodrigues, M.; Kosaric, N.; Bonham, C. A.; Gurtner, G. C. Wound Healing: A Cellular Perspective. *Physiol. Rev.* 2019, 99 (1), 665–706.
- [28] Singer, A. J.; Clark, R. A. F. Cutaneous Wound Healing. *N. Engl. J. Med.* 1999, 341(10), 738–746.
- [29] Young, A.; McNaught, C.-E. The physiology of wound healing. *Surgery (Oxford)* 2011, 29 (10), 475–479.
- [30] Furie, B.; Furie, B. C. Mechanisms of Thrombus Formation. *N. Engl. J. Med.* 2008, 359 (9), 938–949.
- [31] Velnar, T.; Bailey, T.; Smrkolj, V. The Wound Healing Process: An Overview of the Cellular and Molecular Mechanisms. *J. Int. Med. Res.* 2009, 37 (5), 1528–1542.
- [32] Rosa, A. C.; Fantozzi, R. The role of histamine in neurogenic Inflammation. *Br. J. Pharmacol.* 2013, 170 (1), 38–45.
- [33] Broughton, G.; Janis, J. E.; Attinger, C. E. The basic science of Wound healing. *Plast Reconstr Surg* 2006, 117 (7), 12s–34s. (69) Kratoofil, R. M.; Kubes, P.; Deniset, J. F. Monocyte Conversion During Inflammation and Injury. *Arterioscler., Thromb., Vasc. Biol.* 2017, 37 (1), 35–42
- [34] Fathke, C.; Wilson, L.; Hutter, J.; Kapoor, V.; Smith, A.; Hocking, A.; Isik, F. Contribution of bone marrow-derived cells to Skin: Collagen deposition and wound repair. *Stem Cells* 2004, 22 (5), 812–822.
- [35] desJardins-Park, H. E.; Mascharak, S.; Chinta, M. S.; Wan, D. C.; Longaker, M. T. The Spectrum of Scarring in Craniofacial Wound Repair. *Front. Physiol.* 2019, 10, 1.
- [36] Kiwanuka, E.; Junker, J.; Eriksson, E. Harnessing Growth Factors to Influence Wound Healing. *Clin Plast Surg* 2012, 39 (3), 239–248.
- [37] Hajipour, M. J.; Fromm, K. M.; Ashkarran, A. A.; de Aberasturi, D. J.; de Larramendi, I. R.; Rojo, T.; Serpooshan, V.; Parak, W. J.; Mahmoudi, M. Antibacterial properties of nanoparticles. *Trends Biotechnol.* 2012, 30 (10), 499–511.
- [38] Miller, K. P.; Wang, L.; Benicewicz, B. C.; Decho, A. W. Inorganic nanoparticles engineered to attack bacteria. *Chem. Soc. Rev.* 2015, 44 (21), 7787–7807.
- [39] Gupta, A.; Mumtaz, S.; Li, C.-H.; Hussain, I.; Rotello, V. M. Combatting antibiotic-resistant bacteria using nanomaterials. *Chem. Soc. Rev.* 2019, 48 (2), 415–427.
- [40] Liu, Y.; Shi, L.; Su, L.; van der Mei, H. C.; Jutte, P. C.; Ren, Y.; Busscher, H. J. Nanotechnology-based antimicrobials and delivery Systems for biofilm-infection control. *Chem. Soc. Rev.* 2019, 48 (2), 428–446.

- [41] Hajipour, M. J.; Fromm, K. M.; Ashkarran, A. A.; de Aberasturi, D. J.; de Larramendi, I. R.; Rojo, T.; Serpooshan, V.; Parak, W. J.; Mahmoudi, M. Antibacterial properties of nanoparticles. *Trends Biotechnol.* 2012, 30 (10), 499–511.
- [42] Miller, K. P.; Wang, L.; Benicewicz, B. C.; Decho, A. W. Inorganic nanoparticles engineered to attack bacteria. *Chem. Soc. Rev.* 2015, 44 (21), 7787–7807.
- [43] Gupta, A.; Mumtaz, S.; Li, C.-H.; Hussain, I.; Rotello, V. M. Combatting antibiotic-resistant bacteria using nanomaterials. *Chem. Soc. Rev.* 2019, 48 (2), 415–427.
- [44] Liu, Y.; Shi, L.; Su, L.; van der Mei, H. C.; Jutte, P. C.; Ren, Y.; Busscher, H. J. Nanotechnology-based antimicrobials and delivery systems for biofilm-infection control. *Chem. Soc. Rev.* 2019, 48 (2), 428–446.
- [45] Fumakia, M.; Ho, E. A. Nanoparticles encapsulated with LL37 And serpin A1 promotes wound healing and synergistically enhances Antibacterial activity. *Mol. Pharmaceutics* 2016, 13 (7), 2318–2331.
- [46] Mao, C.; Xiang, Y.; Liu, X.; Cui, Z.; Yang, X.; Li, Z.; Zhu, S.; Zheng, Y.; Yeung, K. W. K.; Wu, S. Repeatable photodynamic therapy With triggered signaling pathways of fibroblast cell proliferation and differentiation to promote bacteria-accompanied wound healing. *ACS Nano* 2018, 12 (2), 1747–1759.
- [47] Patel, S. K.; Leong, R.; Zhao, H.; Barone, A.; Casey, D.; Liu, Q.; Burckart, G. J.; Reaman, G. Pediatric Development of Molecularly Targeted Oncology Drugs. *Clin. Pharmacol. Ther.* 2018, 104 (2), 384–389
- [48] Li, S.; Cui, S.; Yin, D.; Zhu, Q.; Ma, Y.; Qian, Z.; Gu, Y. Dual Antibacterial activities of a chitosan-modified upconversion photodynamic therapy system against drug-resistant bacteria in deep tissue. *Nanoscale* 2017, 9 (11), 3912–3924.
- [49] Hu, C.; Zhang, F.; Kong, Q.; Lu, Y.; Zhang, B.; Wu, C.; Luo, R.; Wang, Y. Synergistic chemical and photodynamic antimicrobial Therapy for enhanced wound healing mediated by multifunctional Light-responsive nanoparticles. *Biomacromolecules* 2019, 20 (12), 4581–4692
- [50] Jin, C.; Liu, X.; Tan, L.; Cui, Z.; Yang, X.; Zheng, Y.; Yeung, K. W. K.; Chu, P. K.; Wu, S. Ag/AgBr-loaded mesoporous silica for Rapid sterilization and promotion of wound healing. *Biomater. Sci.* 2018, 6 (7), 1735–1744.
- [51] DeLeo, F. R.; Otto, M.; Kreiswirth, B. N.; Chambers, H. F. Community-associated methicillin-resistant *Staphylococcus aureus*. *Lancet* 2010, 375 (9725), 1557–1568.
- [52] Yan, X.; Fang, W.-W.; Xue, J.; Sun, T.-C.; Dong, L.; Zha, Z.; Qian, H.; Song, Y.-H.; Zhang, M.; Gong, X.; Lu, Y.; He, T. Thermoresponsive in Situ Forming Hydrogel with Sol–Gel Irreversibility for Effective Methicillin-Resistant *Staphylococcus Aureus* Infected Wound Healing. *ACS Nano* 2019, 13 (9), 10074–10084.
- [53] Flemming, H.-C.; Wingender, J. The biofilm matrix. *Nat. Rev. Microbiol.* 2010, 8 (9), 623–633.
- [54] Wang, Y.; Lu, Y.; Zhang, J.; Hu, X.; Yang, Z.; Guo, Y.; Wang, Y. A synergistic antibacterial effect between terbium ions and reduced Graphene oxide in a poly (vinyl alcohol)–alginate hydrogel for Treating infected chronic wounds. *J. Mater. Chem. B* 2019, 7 (4), 538–547.
- [55] Jiang, S.; Ma, B. C.; Huang, W.; Kaltbeitzel, A.; Kizisavas, G.; Crespy, D.; Zhang, K. A.; Landfester, K. Visible light active Nano fibrous membrane for antibacterial wound dressing. *Nanoscale Horizons* 2018, 3 (4), 439–446.
- [56] Mao, C.; Xiang, Y.; Liu, X.; Cui, Z.; Yang, X.; Yeung, K. W. K.; Pan, H.; Wang, X.; Chu, P. K.; Wu, S. Photo-inspired antibacterial Activity and wound healing acceleration by hydrogel embedded with Ag/Ag@ AgCl/ZnO nanostructures. *ACS Nano* 2017, 11 (9), 9010–9021.
- [57] Li, M.; Liu, X.; Tan, L.; Cui, Z.; Yang, X.; Li, Z.; Zheng, Y.; Yeung, K. W. K.; Chu, P. K.; Wu, S. Noninvasive rapid bacteria-killing And acceleration of wound healing through photothermal/photodynamic/copper ion synergistic action of a hybrid hydrogel. *Biomater. Sci.* 2018, 6 (8), 2110–2121.
- [58] Yuwen, L.; Sun, Y.; Tan, G.; Xiu, W.; Zhang, Y.; Weng, L.; Teng, Z.; Wang, L. MoS₂@ polydopamine-Ag nanosheets with Enhanced antibacterial activity for effective treatment of *Staphylococcus aureus* biofilms and wound infection. *Nanoscale* 2018, 10(35), 16711–16720.
- [59] Galandakova, A.; Frankova, J.; Ambrozova, N.; Habartova, K.; Pivodova, V.; Zalesak, B.;

- Safarova, K.; Smekalova, M.; Ulrichova, J. Effects of silver nanoparticles on human dermal fibroblasts and Epidermal keratinocytes. *Hum. Exp. Toxicol.* 2016, 35 (9), 946–57.
- [60] Avalos, A.; Haza, A. I.; Mateo, D.; Morales, P. Interactions of Manufactured silver nanoparticles of different sizes with normal Human dermal fibroblasts. *Int. Wound J.* 2016, 13 (1), 101–9.
- [61] Mahmoudi, M.; Abdelmonem, A. M.; Behzadi, S.; Clement, J.H.; Dutz, S.; Ejtehadi, M. R.; Hartmann, R.; Kantner, K.; Linne, U.; Maffre, P.; Metzler, S.; Moghadam, M. K.; Pfeiffer, C.; Rezaei, M.; Ruiz-Lozano, P.; Serpooshan, V.; Shokrgozar, M. A.; Nienhaus, G. U.; Parak, W. J. Temperature: The “Ignored” Factor at the NanoBio Interface. *ACS Nano* 2013, 7 (8), 6555–6562.
- [62] Sharifi, S.; Behzadi, S.; Laurent, S.; Laird Forrest, M.; Stroeve, P.; Mahmoudi, M. Toxicity of nanomaterials. *Chem. Soc. Rev.* 2012, 41 (6), 2323–43.
- [63] Kramer, A.; Dissemond, J.; Kim, S.; Willy, C.; Mayer, D.; Papke, R.; Tuchmann, F.; Assadian, O. Consensus on Wound Antisepsis: Update 2018. *Skin Pharmacology and Physiology* 2018, 31(1), 28–58.
- [64] Khansa, I.; Schoenbrunner, A. R.; Kraft, C. T.; Janis, J. E. Silver in Wound Care-Friend or Foe?: A Comprehensive Review. *Plastic and reconstructive surgery.* *Global open* 2019, 7 (8), e2390.
- [65] Hadrup, N.; Sharma, A. K.; Loeschner, K. Toxicity of silver Ions, metallic silver, and silver nanoparticle materials after in vivo Dermal and mucosal surface exposure: A review. *Regul. Toxicol. Pharmacol.* 2018, 98, 257–267.
- [66] Fong, J.; Wood, F. Nanocrystalline silver dressings in wound Management: a review. *Int. J. Nanomedicine* 2006, 1 (4), 441–9.f
- [67] Holmes, A. M.; Lim, J.; Studier, H.; Roberts, M. S. Varying the Morphology of silver nanoparticles results in differential toxicity Against micro-organisms, HaCaT keratinocytes and affects skin Deposition. *Nanotoxicology* 2016, 10 (10), 1503–1514.
- [68] Samberg, M. E.; Oldenburg, S. J.; Monteiro-Riviere, N. A. Evaluation of silver nanoparticle toxicity in skin in vivo and Keratinocytes in vitro. *Environ. Health Perspect.* 2010, 118 (3), 407–13.
- [69] Dunn, K.; Edwards-Jones, V. The role of Acticoat with Nanocrystalline silver in the management of burns. *Burns* 2004, 30, S1–S9.
- [70] Hadrup, N.; Sharma, A. K.; Loeschner, K. Toxicity of silver Ions, metallic silver, and silver nanoparticle materials after in vivo Dermal and mucosal surface exposure: A review. *Regul. Toxicol. Pharmacol.* 2018, 98, 257–267.
- [71] Poon, V. K.; Burd, A. In vitro cytotoxicity of silver: implication For clinical wound care. *Burns* 2004, 30 (2), 140–7.
- [72] Nethi, S. K.; Barui, A. K.; Mukherjee, S.; Patra, C. R. Engineered Nanoparticles for Effective Redox Signaling During Angiogenic and Antiangiogenic Therapy. *Antioxid. Redox Signaling* 2019, 30 (5), 786–809.
- [73] Liu, W. J.; Zhang, G. L.; Wu, J. R.; Zhang, Y. L.; Liu, J.; Luo, H. Y.; Shao, L. Q. Insights into the angiogenic effects of Nanomaterials: mechanisms involved and potential applications. *J. Nanobiotechnol.* 2020, 18 (1), 1.
- [74] Patra, C. R.; Kim, J. H.; Pramanik, K.; d’Uscio, L. V.; Patra, S.; Pal, K.; Ramchandran, R.; Strano, M. S.; Mukhopadhyay, D. Reactive Oxygen Species Driven Angiogenesis by Inorganic Nanorods. *Nano Lett.* 2011, 11 (11), 4932–4938.
- [75] Nethi, S. K.; Barui, A. K.; Mukherjee, S.; Patra, C. R. Engineered Nanoparticles for Effective Redox Signaling During Angiogenic and Antiangiogenic Therapy. *Antioxid. Redox Signaling* 2019, 30 (5), 786–809.
- [76] Claffey, K. P.; Brown, L. F.; del Aguila, L. F.; Tognazzi, K.; Yeo, K. T.; Manseau, E. J.; Dvorak, H. F. Expression of vascular Permeability factor/vascular endothelial growth factor by melanoma Cells increases tumor growth, angiogenesis, and experimental Metastasis. *Cancer research* 1996, 56 (1), 172–81.
- [77] Sen, C. K. The general case for redox control of wound repair. *Wound repair and regeneration: official publication of the Wound Healing Society [and] the European Tissue Repair Society* 2003, 11 (6),
- [78] Schafer, M.; Werner, S. Oxidative stress in normal and Impaired wound repair. *Pharmacol. Res.* 2008, 58 (2), 165–71.
- [79] Jo, D. H.; Kim, J. H.; Son, J. G.; Piao, Y.; Lee, T. G.; Kim, J. H. Inhibitory activity of gold and silica Nano spheres to vascular Endothelial

- growth factor (VEGF)-mediated angiogenesis is determined by their sizes. *Nano Res.* 2014, 7 (6), 844–852
- [80] Motterlini, R. Carbon monoxide-releasing molecules (CO-RMs): Vasodilator, anti-ischaemic and anti-inflammatory activities; Portland Press Ltd.: London, United Kingdom, 2007
- [81] Yu, Q.; Han, Y.; Tian, T.; Zhou, Q.; Yi, Z.; Chang, J.; Wu, C. Chinese sesame stick-inspired nano-fibrous scaffolds for tumour Therapy and skin tissue reconstruction. *Biomaterials* 2019, 194, 25
- [82] Lau, P.; Bidin, N.; Islam, S.; Shukri, W.; Zakaria, N.; Musa, N.; Krishnan, G. Influence of gold nanoparticles on wound healing Treatment in rat model: Photobiomodulation therapy. *Lasers Surg. Med.* 2017, 49 (4), 380–386.
- [83] Boink, M. A.; Roffel, S.; Nazmi, K.; van Montfrans, C.; Bolscher, J. G. M.; Gefen, A.; Veerman, E. C. I.; Gibbs, S. The Influence of Chronic Wound Extracts on Inflammatory Cytokine and Histatin Stability. *PLoS One* 2016, 11 (3), e0152613
- [84] Kunkemoeller, B.; Kyriakides, T. R. Redox Signaling in Diabetic Wound Healing Regulates Extracellular Matrix Deposition. *Antioxid. Redox Signaling* 2017, 27 (12), 823–838.
- [85] Chen, X.; Zhou, W.; Zha, K.; Liu, G. H.; Yang, S. H.; Ye, S.N.; Liu, Y.; Xiong, Y.; Wu, Y. C.; Cao, F. Q. Treatment of chronic Ulcer in diabetic rats with self assembling nanofiber gel encapsulated polydeoxy ribonucleotide. *Am. J. Transl Res.* 2016, 8 (7), 3067–3076.
- [86] Uppal, R.; Ramaswamy, G. N.; Arnold, C.; Goodband, R.; Wang, Y. Hyaluronic acid nanofiber wound dressing production, Characterization, and in vivo behavior. *J. Biomed. Mater. Res., Part B* 2011, 97B (1), 20–29.
- [87] Mohiti-Asli, M.; Saha, S.; Murphy, S. V.; Gracz, H.; Pourdeyhimi, B.; Atala, A.; Lobo, E. G. Ibuprofen loaded PLA Nanofibrous scaffolds increase proliferation of human skin cells in Vitro and promote healing of full thickness incision wounds in vivo. *J. Biomed. Mater. Res., Part B* 2017, 105 (2), 327–339
- [88] Wang, Q. X.; Qian, Z. Y.; Liu, B.; Liu, J. L.; Zhang, L.; Xu, J. In Vitro and in vivo evaluation of new PRP antibacterial moisturizing Dressings for infectious wound repair. *J. Biomater. Sci., Polym. Ed.* 2019, 30 (6), 462–485.
- [89] Yang, X.; Yang, J.; Wang, L.; Ran, B.; Jia, Y.; Zhang, L.; Yang, G.; Shao, H.; Jiang, X. Pharmaceutical Intermediate-Modified Gold Nanoparticles: Against Multidrug-Resistant Bacteria and Wound Healing Application via an Electrospun Scaffold. *ACS Nano* 2017, 11 (6), 5737–5745.
- [90] Dhivya, S.; Padma, V. V.; Santhini, E. Wound dressings – a Review. *Biomedicine (Taipei)* 2015, 5 (4), 22–22
- [91] Portela, R.; Leal, C. R.; Almeida, P. L.; Sobral, R. G. Bacterial Cellulose: a versatile biopolymer for wound dressing applications. *Microb. Biotechnol.* 2019, 12 (4), 586–610.
- [92] Panacek, A.; Kvitek, L.; Smekalova, M.; Vecerova, R.; Kolar, M.; Roderova, M.; Dycka, F.; Sebel, M.; Prucek, R.; Tomanec, O.; Zboril, R. Bacterial resistance to silver nanoparticles and how to overcome it. *Nat. Nanotechnol.* 2018, 13 (1), 65–71
- [93] Zenilman, J.; Valle, M. F.; Malas, M. B.; Maruthur, N.; Qazi, U.; Suh, Y.; Wilson, L. M.; Haberl, E. B.; Bass, E. B.; Lazarus, G., AHRQ Comparative Effectiveness Reviews. In *Chronic Venous Ulcers: A Comparative Effectiveness Review of Treatment Modalities*; Agency for Healthcare Research and Quality (US): Rockville, MD, 2013.
- [94] Paredes, J. C. L. I. a. J. A. *Topical Wound Care Treatment and Indications for Their Use*, 4th ed.; Springer International Publishing AG: 2018.
- [95] Azhdarzadeh, M.; Saei, A. A.; Sharifi, S.; Hajipour, M. J.; Alkilany, A. M.; Sharifzadeh, M.; Ramazani, F.; Laurent, S.; Mashaghi, A.; Mahmoudi, M. Nanotoxicology: advances and pitfalls in research Methodology. *Nanomedicine* 2015, 10 (18), 2931–2952
- [96] Payne, J. L.; Ambrosio, A. M. Evaluation of an antimicrobial Silver foam dressing for use with V.A.C. therapy: morphological, Mechanical, and antimicrobial properties. *J. Biomed. Mater. Res., Part B* 2009, 89B (1), 217–222.