



HAL
open science

State-of-the-Art and Future Challenges of Smart Wound Dressings for Diabetic Foot Ulcer Treatment

Sabine Szunerits, Rabah Boukherroub

► To cite this version:

Sabine Szunerits, Rabah Boukherroub. State-of-the-Art and Future Challenges of Smart Wound Dressings for Diabetic Foot Ulcer Treatment. *Advanced NanoBiomed Research*, 2024, 10.1002/anbr.202400040 . hal-04665117

HAL Id: hal-04665117

<https://hal.science/hal-04665117v1>

Submitted on 30 Jul 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

State-of-the-Art and Future Challenges of Smart Wound Dressings for Diabetic Foot Ulcer Treatment


Sabine Szunerits* and Rabah Boukherroub

The slow healing process of diabetic wound due to persisting infections in wound bed, owing to hyperglycemia, makes the search for efficient treatments pending. While it is complicated to increase the wound closure rate in diabetic-related wounds due to the complex pathology, the treatment of such wound with hydrogels is seen as a promising approach and pursued over the years. However, where is this research currently standing in terms of clinical translation of these different multifunctional and stimuli-responsive hydrogel bandages to accelerate diabetic foot ulcer healing and help to improve the life of the patients and the future of diabetic wound management? This perspective article will review some of the most important advancements in the field and will conclude with some perspectives, considered as relevant in the clinical context.

1. Introduction

The skin is the first fence to external invasion. Upon injury, several overlapping (Figure 1A) but independent phases are involved in wound closure comprising the release of growth factors by the newly formed cells, stimulating the formation of a new connective tissue and microscopic blood vessels on the surfaces of the wound. This process is complemented with a remodeling period during which the fibronectin-rich matrix is replaced with a stronger collagenous matrix. Normal wounds resolve this cascade of processes within longest some weeks not exceeding 2–3 months. In the case of diabetic foot ulcers (DFU), this process exceeds three months due to chronic inflammation. Indeed, hyperglycemia promotes bacterial colonization and biofilm formation, worsening the unstable wound environment. In addition, inflammatory cells are a source of excessive reactive oxygen species (ROS), hindering re-epithelization.

S. Szunerits, R. Boukherroub
Univ. Lille
CNRS
Univ. Polytechnique Hauts-de-France
UMR 8520 - IEMN
F-59000 Lille, France
E-mail: sabine.szunerits@univ-lille.fr

 The ORCID identification number(s) for the author(s) of this article can be found under <https://doi.org/10.1002/anbr.202400040>.

© 2024 The Author(s). Advanced NanoBiomed Research published by Wiley-VCH GmbH. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

DOI: 10.1002/anbr.202400040

In parallel, vascular complications of diabetic patients often result in deficiencies in oxygen and nutrient delivery to the wound bed.

The primary and classical clinical treatment of diabetic ulcers consists in protecting the wound with bandages and wound debridement (Figure 1B). Currently, gauze is mostly used as wound bandage, being inexpensive and convenient. The use of gauze is challenged by several practical obstacles. In fact, these bandages neither aim in accelerating wound healing, nor do they consider bacterial infection control of reactive oxygen species (ROS) concentration level and/or impaired angiogenesis or how to provide the wound with moisture.

Furthermore, during the change of these dressings, secondary injuries often result, as the gauze dressing adheres to the wound after absorbing wound exudate. In light of these diverse challenges, various research teams have tried to come up with innovative approaches to overcome these pending issues (Figure 1C). Functional hydrogels and hydrogel-based scaffolds are the most widely studied wound dressings in this respect and several review articles are devoted to the development of multifunctional hydrogels demonstrating enhanced wound healing ability.^[1] Hydrogels are 3D networks that can retain high water contents. This class of wound dressings combines many advantages for the treatment of DFU. The high water content along with the good physicochemical/mechanical characteristics makes hydrogels advantageous compared to more classical wound bandages. The 3D structure of hydrogels allows furthermore to be a drug reservoir for antibacterial agents, ROS scavenging compounds, and/or promising anti-angiogenesis drugs. While priority was given indeed over a long time to the development of antibacterial hydrogels for DFU,^[2] pro-angiogenesis,^[3] and pro-healing became a priority in recent years and considered important to be addressed as additional features. In addition, advances in hydrogel technology allow the preparation of adhesive hydrogel bandages with a structural resemblance to human tissue and minimal localized secondary injury issues.^[4] Inspired by the adhesive nature of catechol and amines in mussel adhesive proteins, the use of polydopamine is one of the most widely preferred component of such hydrogel bandages.^[5] These chemical functions endow the hydrogel with direct adhesion to the skin and easy release without damage. The use of supramolecular cascade reaction, through the cooperative interactions of chitosan, sulfobutylether- β -cyclodextrin, ferrous ions, and glucose oxidase, is another way to allow for improved DFU healing. The increased glucose level in diabetic patients activates the generation of hydroxyl radicals via the

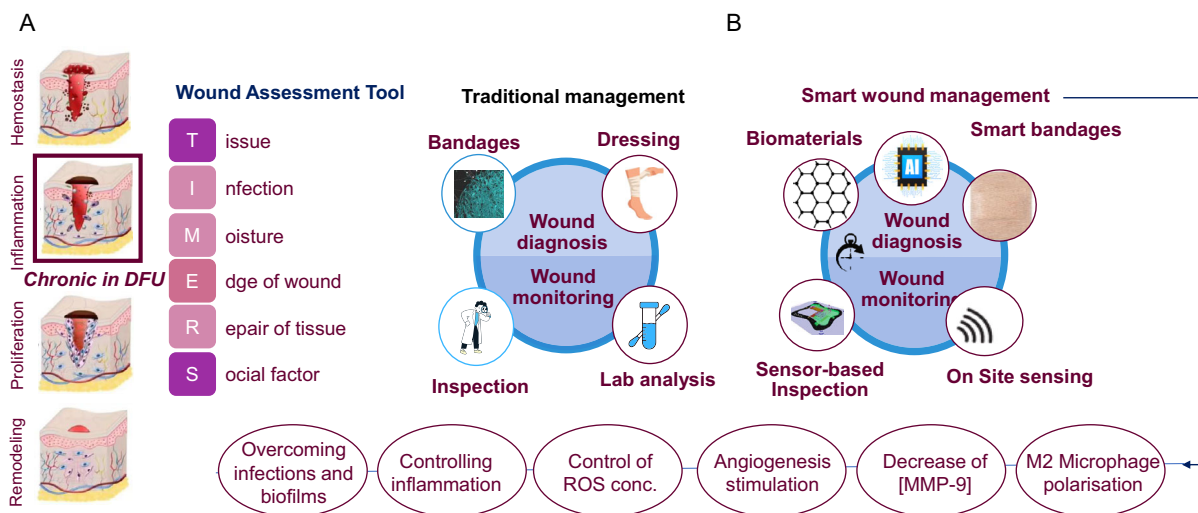


Figure 1. Different levels to promote healing of diabetic foot ulcers (DFU): A) Stages of wound healing and current wound assessment strategy (<https://www.credihealth.com/blog/stages-of-healing-a-wound>). B) Traditional versus smart wound management together with parameters to be integrated into smart wound bandages: preventing bacterial attachment and biofilm formation *via* anti-fouling and super-hydrophilic materials as well as thermal ablation of bacteria; overcoming wound infections and inflammation *via* antibiotics and alternatives, such as metal nanoparticles, peptides, and increase of cellular stress; removing excess ROS by ROS scavengers; promoting angiogenesis with growth factors, stem cells, extracellular vesicles (EV); decrease of MMP-9 levels in wound bed through MMP-9 specific inhibitors, triggered macrophage polarization, controlled and stimulated drug delivery, and wound monitoring. On site sensing image, Reproduced under the terms of the CC-BY 4.0 license. Copyright 2022, The Authors. Published by Nature Portfolio.

formation of hydrogen peroxide by embedded glucose oxidase.^[6] The hydroxyl radicals in parallel initiate a radical polymerization to form hydrogel network structures for protection and bacteria ablation, while inhibiting resistant bacterial infection.

Advances made in the last 2 years in the field of hydrogel-based dressings will be the focus of this perspective article with the aim to highlight where the major breakthroughs have taken place. As the field is highly diverse, the article is structured around the “function” of the hydrogels with the development of 1) antibacterial, 2) anti-inflammatory, 3) antioxidant, and 4) pro-angiogenesis hydrogels being considered in more details (Figure 1). Hydrogels with controlled delivery of therapeutics targeting these four actions are the main focus of the discussion here. Advances in stimulated drug release from such multifunctional bandages will be highlighted. More lately, triggering macrophage polarization was added to the list of important features to be integrated in the concept of DFU wound healing along with the possibility to monitor wound healing via digital, wearable sensors integrated into the wound bandages.

2. Antibacterial Hydrogels for DFU Treatment

Encapsulation of antimicrobial drugs into hydrogels mostly via electrostatic interactions remains the preferred strategy. The increased issue with antibiotic resistance makes the search for alternatives pending, with metallic (silver, zinc, copper) nanoparticles (NPs) being widely explored for potential antibacterial applications. With silver NPs being categorized as biocide in the EU,^[7] other nanostructures such as ZnO NPs are less cytotoxic, with ZnO nanostructures having great potential to positively impact wound healing. It was as early as 2012, when Kumar et al. evaluated a ZnO-NPs-loaded chitosan hydrogel for

the treatment of DFU in human patients.^[8] In a randomized controlled clinical study on 26 T2D patients with foot ulcers, it was found that the patient group treated with the ZnO NPs/chitosan bandage (G1; $n = 16$) exhibited a healing time of 48 days with 75% wound closure, as compared to the control group (G2; $n = 10$) having received a ZnO calcium alginate without bandage, with an average healing time of 72 days and 71% wound closure.

An intrinsic antibacterial hydrogel-forming polymer is chitosan with high adsorption capacity, being biocompatible, non-immunogenic, and of low cost.^[9] The cationic nature of chitosan is the underlining reason for its antibacterial activity. The efficacy and safety of chitosan-based dressings in the treatment of diabetic wounds have been undertaken by the team of Moravvej et al. for example.^[10] In their study, 25 patients with chronic wounds were treated with either chitosan or Acticoat dressings. Reduction of infection was slightly better with chitosan (78.1%) compared to Acticoat (74.1%), with chitosan overcoming the issue of the need for Ag colloids.

More recently, chitosan nanofiber patches, produced by electrospinning, have been applied for DFU treatment.^[11] The porous structure of the resulting chitosan-based nanofibers not only removed liquid from the wound efficiently and had oxygen permeability, but gradually depolymerized and released fibroblast proliferation *N*-acetyl—D-glucosamine. The positive charge of chitosan accounts for the antibacterial character with an enhanced blood coagulation behavior, owing to its activating power of platelets in blood vessels.

In the context of DFU, injectable therapeutic hydrogels represent an innovative option for wound repair. Such gels are excellent scaffolds for drugs, which can be released overtime and improve treatment outcomes. Garcia-Fernandez et al. investigated, for example, the efficacy of chitosan/citric acid, beta-cyclodextrin polymer (poly(cyclodextrin citrate) [PCD])/cinnamaldehyde-based

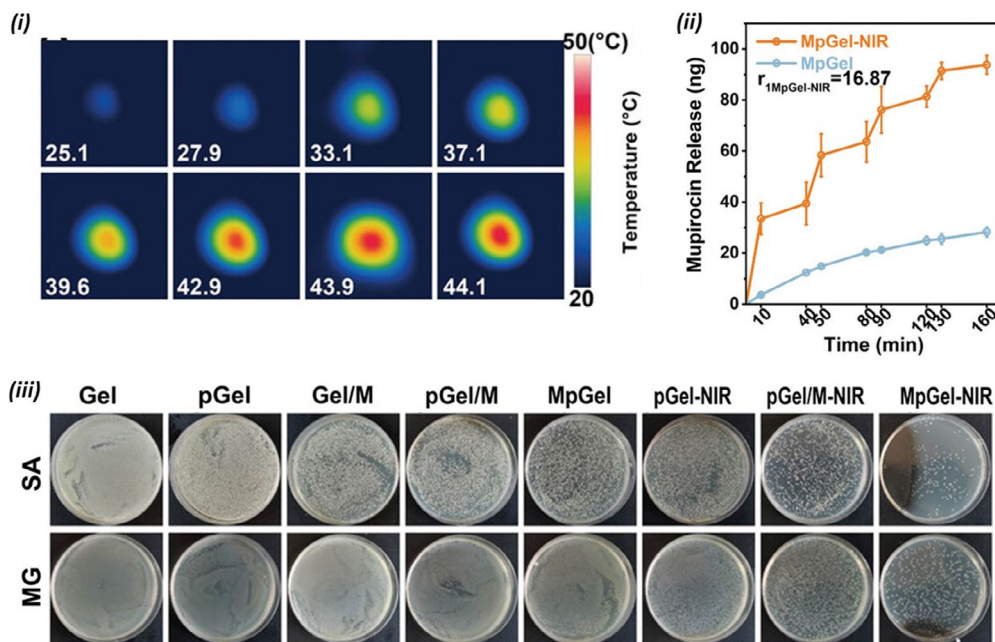


Figure 2. Photothermal activatable hydrogel with antibacterial functions: i) temperature variation overtime for a polydopamine/reduced graphene oxide (rGO) hydrogel (pGel); ii) mupirocin (Mp) release rate of different hydrogel formulations; iii) antibacterial properties against *Staphylococcus aureus* (SA) and *Escherichia coli* (MG) bacteria. Reproduced under the terms of the CC-BY 4.0 license.^[13] Copyright 2023, The Authors. Published by Wiley-VCH GmbH.

injectable hydrogel formulations.^[12] The choice of PCD rather than cyclodextrin was made owing to its enhanced solubility properties. Cinnamaldehyde, a natural product, in contrast has a high activity against gram-positive and gram-negative bacteria, and could be one of the means to selectively kill *Staphylococcus aureus* (SA) in the wound bed.

Photothermal-based concepts are elegant ways to improve wound management when implemented with thermal-sensitive materials, such as polydopamine/reduced graphene oxide (rGO) matrixes, noted as pGel, where antibiotics like mupirocin (Mp) can be released through customized demand (Figure 2).^[13] The photothermal activity of the pGel was clearly evidenced, reaching a temperature of almost 45 °C after 80 min under near-infrared (NIR) irradiation. Preloading an antibiotic like mupirocin onto rGO followed by the hydrogel formation (noted as MpGel) resulted in a gel with limited passive drug release and obvious enhanced release capacity under NIR irradiation. The antibacterial properties were furthermore investigated on gram-positive SA and gram-negative *Escherichia coli* MG1655 (MG) bacteria strains (Figure 2). The released mupirocin was most sufficient on SA when the drug was released under NIR irradiation from MpGel. The effect on Gram-negative bacteria was however limited. This work is interesting as it translates the multifunctional bandage urgently needed in this area to a full-stage wound healing for the treatment of infected DFU.

3. Antioxidant/Anti-Inflammation Hydrogels for DFU Treatment

The main difference of diabetic wounds and some others is that the hyperglycemic environment increases the risk of infections,

inducing an evolution into a chronically inflamed wounds and excessive production of matrix metalloproteinases (MMPs).^[1c] Inflammation is the second stage in the four-step wound healing process, important for the removal of debris and for the ablation of bacteria. Excessive inflammation will however result in high oxidative stress with an increase in the production of ROS destroying cells or oxidize DNA and protein, effecting cell migration and endorsing angiogenesis, which can arrest the wound healing process. It has been reported that the concentration level of H₂O₂ in plasma is between 1 and 5 μM, while under inflammation conditions, the concentration can exceed 50 μM.^[14] The formed free radicals can be trapped and neutralized by antioxidant reagents, such as polyphenol,^[15] or curcumin,^[16] to promote wound healing. However, these therapies are not effective. The integration of magnesium ascorbyl phosphate has lately proven to scavenge ROS efficiently and was considered as potential agent in a gelatin-ascorbyl phosphate scaffold to accelerate diabetic wound healing.^[17]

Another way to improve wound healing is to control Transforming Growth Factor Beta (TGF-β) signaling, as TGF-β1 is related with tissue inflammation. The reduced endothelial cells' migration leads to delayed angiogenesis. Reducing the delirious impact of TGF-β1 via TGF-β inhibitors or anti-TGF-β antibodies are strategies to be considered, but have shown low efficacy in clinical setting. It is believed that, while lowering TGF-β1 and interfering with the TGF-β1/p38 pathway, it also acts on the wound healing critical TGF-β1/Smad2/3 pathway.^[18]

A recent study^[19] investigated temperature-sensitive ROS-scavenging hydrogels loaded with PTβR21, a TGF-β inhibitor (Figure 3). With a thermal-transition temperature of 17.8 °C, the solution is easily injectable at room temperature, and solidified at body temperature. Degradation studies in the presence of

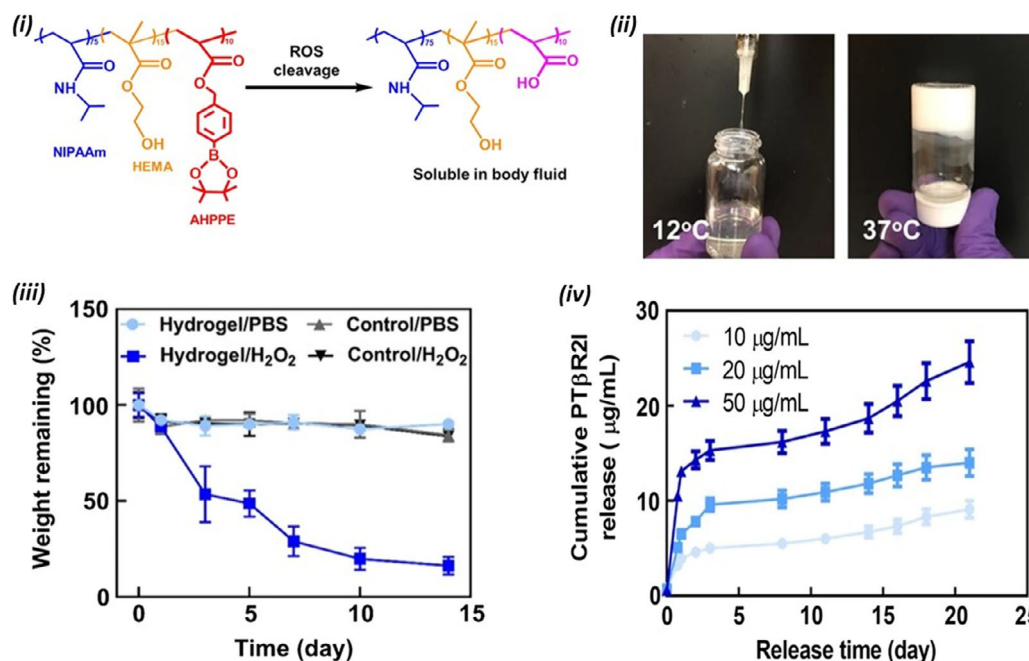


Figure 3. Reactive-oxygen-species-responsive PTβR21-peptide-loaded injectable hydrogel: i) degradation mechanism of poly[(N-isopropylacrylamide)-co-(2-hydroxyethylmethacrylate)-co-[4-(hydroxymethyl)-phenylboronic acid, pinacol ester] acrylate (NIPAAm-co-HEMA-co-AHPPE); ii) image of temperature-dependent solid-gel formation; iii) degradation of the NIPAAm-co-HEMA-co-AHPPE hydrogel and a non-ROS-responsive hydrogel in the presence/absence of 1 mM H₂O₂; and iv) cumulative release of PTβR21 overtime from the hydrogel. Reproduced under the terms of the CC-BY 4.0 license.^[19] Copyright 2023, The Authors. Published by Nature Portfolio.

H₂O₂ revealed that the hydrogel displayed a significantly higher weight loss compared to a control hydrogel. The hydrogel exhibited good biocompatibility and comparable F4/80+ macrophage density after 7 days implantation. PTβR21 was gradually released during 21 days after an initial burst observed on the first day.

4. Hydrogels with Pro-Angiogenic Modulating Properties

Vascular endothelial growth factor (VEGF) is a key mediator-modulating angiogenesis and vasculogenesis, and increases blood vessel permeability. With cutaneous injury, the immediate change to hypoxic conditions induces various cells to release VEGF. A topical VEGF application could indeed accelerate chronic wound healing in diabetic mice,^[20] and improve clinical use.^[21] NIR-electrospun polycaprolactone fiber networks integrated within methacrylic anhydride gelatin-based hydrogels loaded with deferoxamine displayed for example clear angiogenesis and re-epithelization of diabetic wounds. Cells attached easily to the fibers in the dressing and grew along the fiber direction. The large pore size of >500 μm of the network allowed cells to penetrate the hydrogel.^[22] Self-assembling peptide hydrogels, made out of multiple short repetitive peptide domains,^[23] have shown furthermore promising growth factor delivery characteristics. The effect of the pro-angiogenic SLaN peptide against the commercial product PuraMatrix and a non-functionalized non-bioactive control sequentially similar to SLaN, K2, on wound healing was lately investigated.^[24] The effects of wound contraction

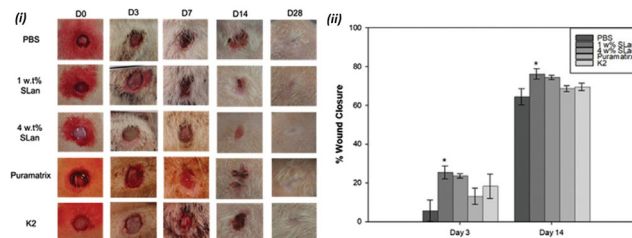


Figure 4. Pro-angiogenic self-assembling peptide hydrogels SLaN for the treatment of diabetic wound ulcer: i) photographs of wound closure; ii) wound closure percentage at day 3 and day 14. Reproduced with permission.^[24] Copyright 2022, Wiley-VCH GmbH.

and closure for the different treatments are depicted in **Figure 4**. While each treatment condition resolved wound closure after 28 days, treatment with a low concentration of SLaN significantly accelerated wound closure at 3, 7, and 14 days after injury. This suggests that such materials can be used to initiate wound healing.

5. Hydrogels with MMP Inhibition Properties

Metal-dependent endopeptidases (MMPs) play a significant role in the process of the repair of DFUs being involved in the migration of keratinocyte. On the one hand, re-epithelialization requires MMP-7, and wound closure MMP-3, while angiogenesis is regulated by MMP-12. MMP-9 has shown, on the other hand,

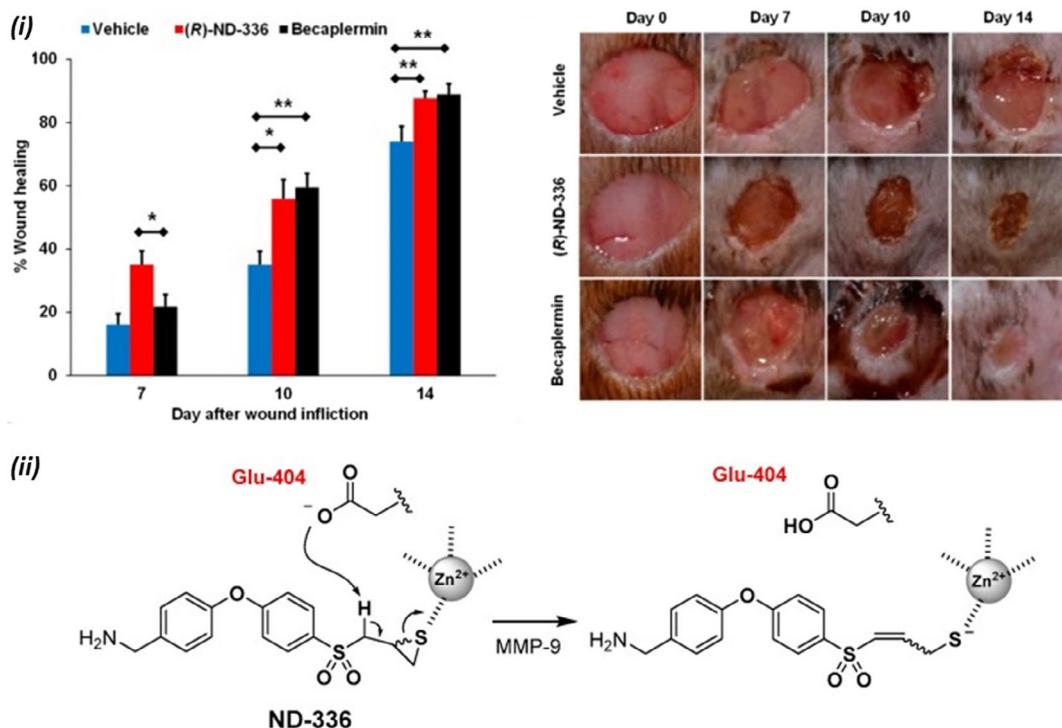


Figure 5. MMP-9 inhibiting actions of (R)-ND-336: i) wound healing capacity of (R)-ND-336 (red), becaplermin (black), and vehicle (water) (blue) of wounds in diabetic mice treated topically 1 day after wound infection with 5 $\mu\text{g day}^{-1}$ (becaplermin), 50 $\mu\text{g day}^{-1}$ (R)-ND-336, or with control (water) for 2 weeks (* $p < 0.05$, ** $p < 0.01$). ii) Inhibition mechanism of (R)-ND-336 due to thiolate formation coordinating with Zn^{2+} tightly and irreversibly. Reproduced with permission.^[26] Copyright 2018, American Chemical Society.

detrimental effects in the prolongation of wound healing. Selective inhibition of MMP-9 would be thus a good approach to accelerate wound healing.^[25] Small molecule inhibitors, such as 2-[[[(4-Phenoxyphenyl)sulfonyl]methyl]thiirane (SB-3CT) and (R)-ND-336 with inhibition constants of 400 and 19 nM, respectively, have been proposed recently for MMP-9 inhibition (Figure 5).^[25b,26] An evaluation of (R)-ND-336 and becaplermin, the only FDA-approved drug for the treatment of DFUs, demonstrated that the former had superior efficacy at early stage of the wound treatment, while becaplermin accelerated wound healing at later days. The effectiveness of (R)-ND-336 is due to selective and complete MMP-9 inhibition (Figure 5), as the degradation product of (R)-ND-336 coordinates with the zinc active site of MMP-9 in an irreversible manner. (R)-ND-336 is in contrast a poor inhibitor for MMP-8. In contrast, becaplermin only decreases the MMP-9 activity, with no complete inhibition.

6. Hydrogels with Triggered Macrophage Polarization for DFU Treatment

Macrophages and their phenotypes have been found to play an important role in the inflammatory stage. M1 macrophages trigger the release of pro-inflammatory cytokines, while M2 macrophages are present during skin remodeling.^[27] The M1-like phenotype holds thus a critical role in the alteration of the immunomodulatory balance, while the M2-like phenotype is advantageous for rapid angiogenesis and vascularization. M1 to M2

macrophages conversion is important to accelerate wound healing and is more and more part of the properties investigated when reporting on hydrogel bandages.^[4b,28] Huang and co-workers looked into this matter more closely *via* the utilization of a high-molecular-weight hyaluronic acid (HA) hydrogel mixed with poly(vinyl alcohol) and cross-linked with Cu^{2+} .^[28b] The developed hydrogel showed favorable macrophage polarization, with additional reduced vascular damage, resulting in improved wound healing. The degradable HA nanofibrous hydrogel within 3 days was likewise able to promote the transformation of gathered M1 macrophages to the M2 phenotype.^[28b] As seen in Figure 6A, Fe^{3+} -cross-linked gels, formed from HA and 2-(methylthio) ethylamine, via a condensation reaction were completely degraded after 3 days and showed improved wound closure after 15 days. This was partially due to the antioxidant properties, but also to the capability of macrophage phenotype switching. M2 macrophage polarization has shown to be also promoted by exosomes (Exos) from human-adipose-derived mesenchymal stem cells (MSCs)^[29] or blood-platelet-derived extracellular vesicles (pEVs).^[30] This poses the question of how such biological drugs can be administered to the wound, and their loading and release strategies become central.

The porous structure of hydrogels makes them ideal scaffolds for drug loading including biological-derived therapeutics such as protein drugs and live cells.^[31] Indeed, insulin and L929 fibroblasts loaded hydrogels were considered as early as 2017 as bioactive dressings for diabetic wound healing.^[31]

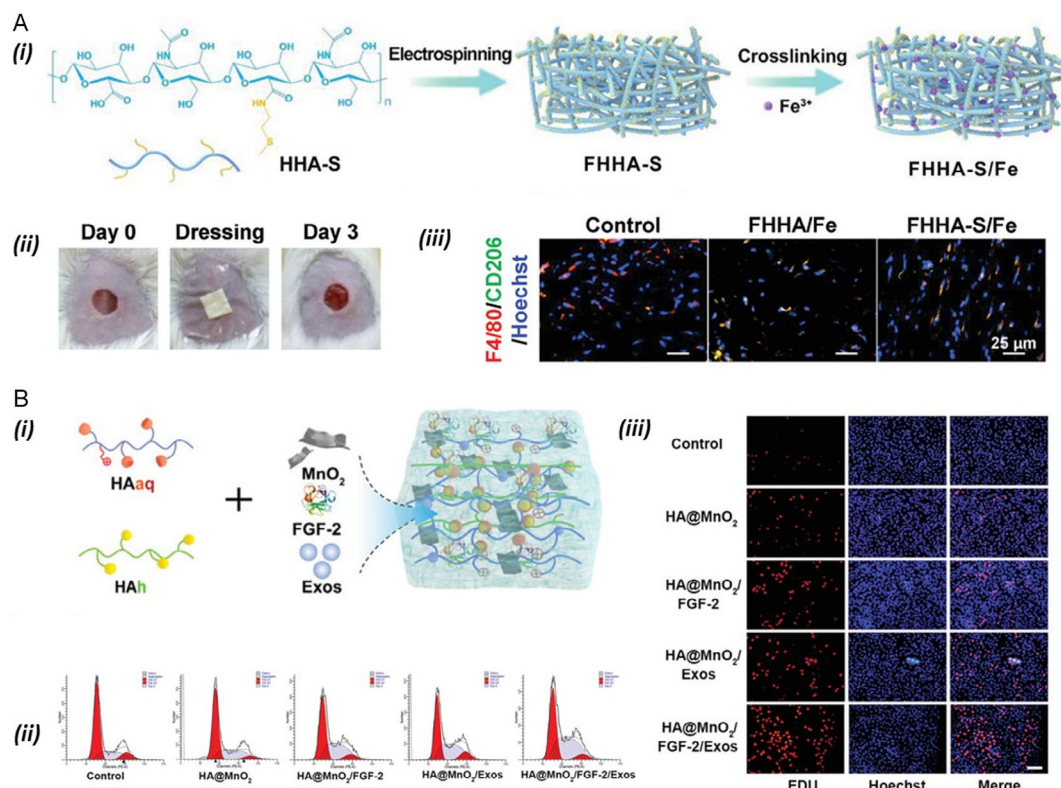


Figure 6. Multifunctional hydrogel. A) i) Illustration of the synthesis of an absorbable iron-chelated hyaluronic-acid-based fiber mat together with ii) images of full thickness wounds at day 0 and day 3 showing that the dressing has been dissolved. iii) Fluorescence images of wounds treated with different hydrogels stained with F4/80 (red) and Hoechst (blue). Reproduced with permission.^[4b] Copyright 2020, Wiley-VCH GmbH. B) i) Formation of HA@MnO₂/FGF-2/Exos hydrogel and using a convenient mixed injection to cover a wound with an HA@MnO₂/FGF-2/Exos hydrogel dressing tightly. ii,iii) Cell proliferation determined by i) flow cytometry and ii) EDU assay of HSFs and primary human umbilical vein endothelial cells in presence of different hydrogels. Reproduced under the terms of the CC-BY 4.0 license.^[32] Copyright 2021, The Authors. Published by Royal Society of Chemistry.

Controlled release of fibroblast growth factor fibroblast growth factor 2 (FGF-2) and M2-derived Exos-loaded injectable hydrogel based on HA composite gel, HA@MnO₂/FGF-2/Exos, was reported recently.^[32] The hydrogel was formed by reaction of hydrazide-grafted HA (HAh), with aldehyde-grafted HA (HAA) and a mixed injection procedure to produce the hydrogel dressings (Figure 6B). The positively charged quaternary ammonium groups in the dressing are responsible for the antibacterial effect, while the MnO₂/ε-polylysine (PL) nanosheets convert harmful H₂O₂ produced in the wound to O₂ important for wound healing.^[32] Flow cytometry and staining assays (Figure 6B) were performed to assess cell proliferation of different hydrogel formulations compared to a control, and indicated increased cell proliferation upon treatment with the HA@MnO₂/FGF-2/Exos hydrogel group.

Next to fibroblasts, mesenchymal stromal cells (MSCs) are being more widely explored, owing to their regenerative properties.^[30] Although MSCs and their secreted cytokines decrease oxidative stress and stimulate wound angiogenesis, their biological activity is compromised by direct injection, hindering their direct therapeutic effect. Hydrogels provide shelter for stem cells, but require innovative strategies for

their release. A hydrolytically degradable ester linkage was, for example, proposed as a strategy for engineering a synthetic hydrogel with adjustable in vivo degradation rates to deliver MSCs.^[33]

The use of platelet-rich plasma (PRP)^[34] for DFU can be seen as a ground-breaking advancement in the last years as they possess chemotactic and mitogenic characteristics, acting as a growth factor agonist. PRP is obtained from the patients' plasma with platelet concentrations reaching $\approx 0.5 \times 10^{11}$ platelets per unit containing clotting and growth factors, including vascular endothelial factor and VEGF, as well as insulin-like growth factor. All of these growth elements promote quick wound healing.^[28a,35] New insights into PRP mechanisms revealed that the extracellular vehicles released from activated platelets participate in tissue repair. For example, it was demonstrated lately that platelet-derived extracellular vesicles (pEVs) can be loaded into rGO-impregnated gelatin-alginate (GelAlg)-based hydrogel bandages.^[28a] Using a migration assay, it could be shown that pEVs loaded GelAlg@rGO hydrogels considerably improved cell migration (Figure 7). Upon exposure of GelAlg@rGO-pEV to NIR light (2 W cm^{-2}), the wound area became significantly smaller after 14 days (Figure 7).

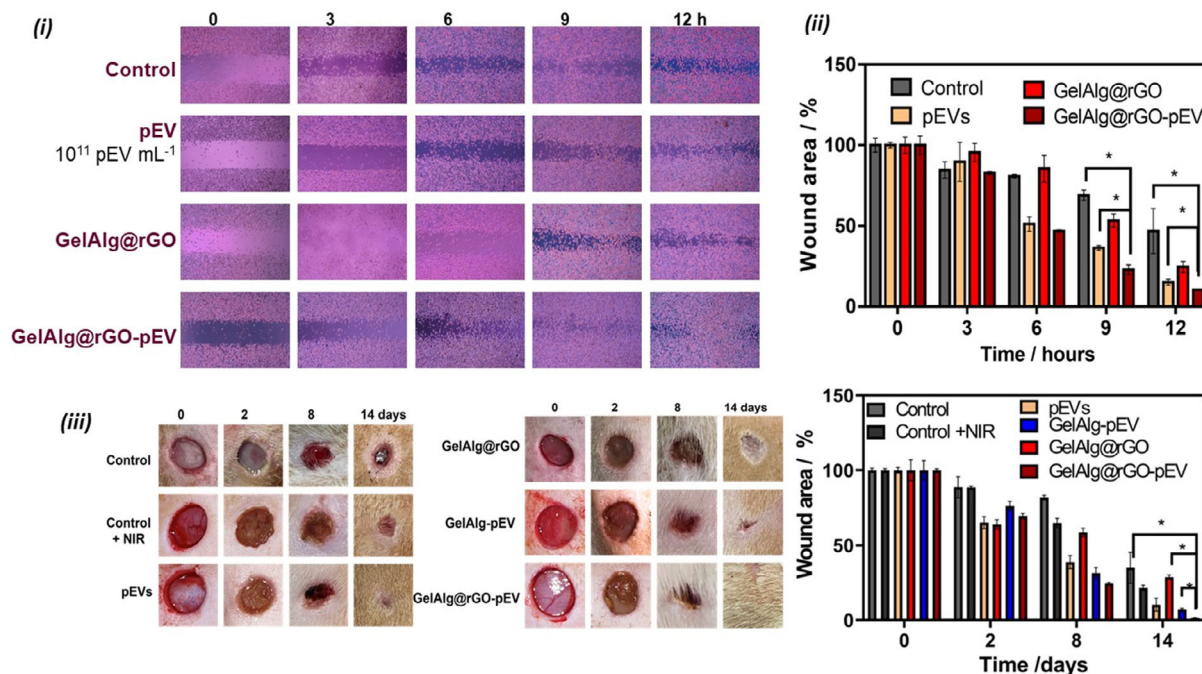


Figure 7. Extracellular vehicles (EVs)-loaded graphene oxide (rGO)-impregnated gelatin–alginate (GelAlg)-based hydrogel: i) in vitro wounds scratch assay based on the investigation of cell migration of L929 cells cultured in phosphate-buffered saline (PBS) (negative control), and in presence of pEV (10^{11} pEV mL $^{-1}$) as well as GelAlg@rGO and GelAlg@rGO–pEV (10^{11} pEV mL $^{-1}$) upon one time 5 min NIR irradiation (808 nm, 2 W cm $^{-2}$); ii) wound area after 12 h; and iii) wound healing rate determined on rats upon treated with different scaffolds and PBS (control) for 14 days and one time 5 min NIR irradiation. Reproduced under the terms of the CC-BY 4.0 license.^[28a] Copyright 2023, The Authors. Published by Springer Nature.

7. Wound Monitoring with Hydrogel Wound-Dressing Sensors

There is lack of comprehensive work of theranostic hydrogel-based wound dressings that incorporate treatment functions next to wound environment monitoring. Early identification that a

wound is not healing is however of significant importance to limit the installation of a chronic nonhealing wound.^[36] With the emergence of flexible electronics diagnostic concepts, real-time monitoring of physicochemical markers (e.g., temperature, pH, humidity, etc.) as well as biological biomarkers (e.g., inflammatory factors, protein-digesting enzymes such as

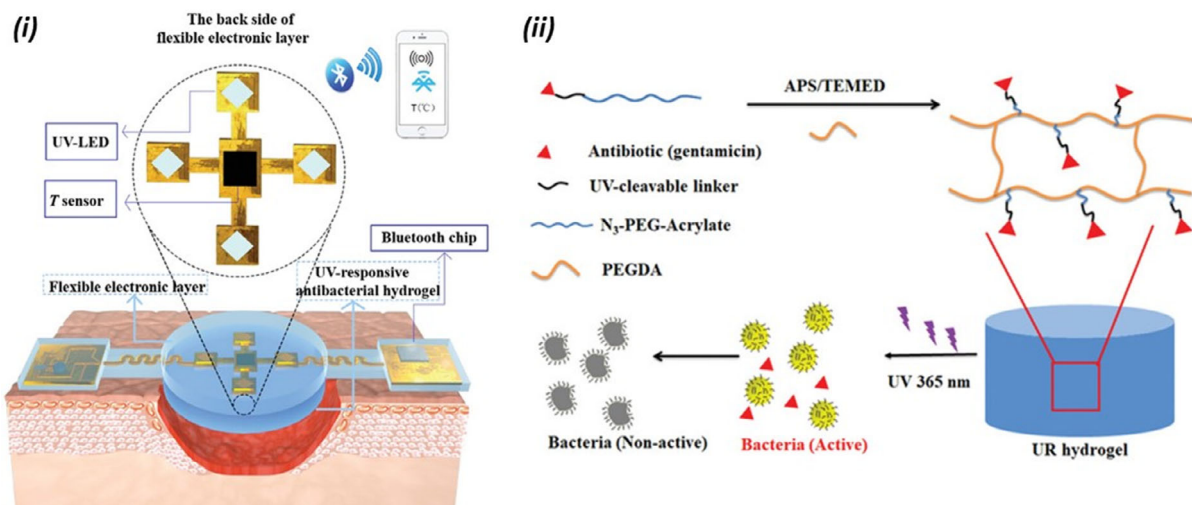


Figure 8. Theranostic wound bandage such as the electronics-integrated wound dressing for controlled release of antibodies upon wound temperature increase. i) Schematics of wound dressing with polydimethylsiloxane-encapsulated flexible electronics for temperature control and UV-LEDs (365 nm) to trigger antibiotic release from UV-responsive gels. ii) Formation of the hydrogel, with gentamicin covalently linked to the PEG-based hydrogel through a UV-cleavable group. Reproduced under the terms of the CC-BY 4.0 license.^[40] Copyright 2020, The Authors. Published by Wiley-VCH GmbH.

MMPs, etc.) are at the forefront of the next generation of wound healing bandages for DFU. Mostafalu et al. reported already in 2018 on a flexible pH sensor to monitor wound infection together with a thermoresponsive drug-release patch interconnected with a flexible microheater.^[37] A large step was recently made by Gao et al. using a flexible multiplexed approach for in situ wound monitoring that integrates temperature, pH, and biomarkers sensing.^[38] Our team recently validated the possibility to sense active MMPs-9 in simulated wound fluids using aptamer-modified graphene-based field effect transistor (gFET) transducer.^[39] However, the real connection with hydrogels and drug release seems less exploited still and only some attempts to monitor the wound status in real time with follow-up treatment are reported. A flexible electronics-integrated wound dressing, comprising a temperature sensor together with an on-demand treatment capacity via an ultraviolet-responsive antibacterial hydrogel, was lately described by Pang et al.^[40] The polyethylene glycol (PEG) based hydrogel consists of azide-PEG5000-acrylate to which gentamicin (GS) was conjugated by a UV-cleavable nitrobenzyl linker. This GS-linker-PEG-acrylate prodrug was then cross-linked to form a hydrogel. Once the wound temperature was higher than the threshold value of 40 °C, the antibiotic release was triggered by UV-light emitting diodes (LEDs) (Figure 8). Self-healing dressings with antibacterial activity and wound monitoring via sensors, a concept proposed by Haick and co-workers, are easily translatable to DFU.^[41] The proposed elastomer based on cetyltrimethylammonium bromide as antibacterial agent helped in contracting wound edges, while the integrated temperature, pH, and glucose level sensors underlined the effective wound healing.

8. Conclusion

About 5% of patients with diabetes are expected to develop diabetic foot ulcers (DFUs) with about 1% ending up with amputation. DFU remains thus an important complication of diabetics being responsible for more hospital admission. DFUs are certainly a result of poor glycemic control, resulting in peripheral vascular complications and negatively influencing wound closure, due to installation of prolonged inflammation and infections of the wound bed. Intersectoral approaches are believed to have the best outcome to delay or even prevent DFU development with research on hydrogel bandages shown to be most promising. While a multitude of hydrogel formulations has been reported so far, the development of multifunctional bandages with stimuli-responsive drug release capability is certainly the most promising field at present. Precise therapeutic deliveries to control ROS concentrations, promote angiogenesis, ablate bacterial colonies, and/or promote M2 macrophage polarization are current targets of therapeutic bandages. Microneedle-based hydrogels as well as hydrogel foams might be the main future players in this field. These materials have plenty of advantages over more traditional hydrogel bandages, but work in this area is still limited. The use of microneedles allows penetrating the wound bed more deeply without causing pain and can deliver drugs to the different layers of the dermis. The limitations of their wider use are related to the often-poor mechanical properties of the microneedles system and the limited amount of drugs

delivered. Hydrogel foams are a class of microporous materials where the dispersed phase is a gas and the continuous one the hydrogel. With porosities reaching >64% and pore sizes exceeding 10 µm, these “medial sponges” are believed to help in wound cleaning and are gaining popularity. Such hydrogels are susceptible to breakage. It is thus of high importance to ensure the structural integrity of hydrogel-based wound bandages, with self-healing hydrogels being one way toward this goal. Finally, theranostic approaches are believed to be the future of intelligent wound dressings. Passive wound dressing cannot monitor the wound healing stage in real time, which may result in wrong therapeutic options. Smart bandages, with the capabilities of monitoring biomarkers and a therapeutic “closed-loop” wound management ability, are emerging and expected to reevaluate the field of wound care to the next level.

What has been largely neglected is the role of the skin microbiome in wound healing.^[42] With around 1000 bacteria species on the skin, some subsets of organisms are favored over others. Perturbation of this epidermal ecosystem can interfere with healing of chronic wound such as DFU. While determination of the specific bacteria involved in chronic wounds remains challenging, administration of commensal bacteria enables to clear inflammation-initiating species such as SA.^[42b,43] The challenge remains to selectively abate skin pathogens without harming the commensal skin bacteria. Bacteria-tagged endolysins, such as XZ.700 enzymes that lyse the cell walls of bacteria when imbedded into hydrogel matrixes, might be considered to be loaded into the next generation of smart bandages and might lead to insights of such novel therapeutic targets.

Acknowledgements

This work received financial support by EuroNanoMed III via the G-Skin project. [Correction added on 4 July 2024, after first online publication: The figure 1 was updated.]

Conflict of Interest

The authors declare no conflict of interest.

Keywords

diabetic foot ulcers, hydrogels, treatments

Received: March 15, 2024

Revised: May 22, 2024

Published online:

- [1] a) Y. Liang, J. He, B. Guo, *ACS Nano* **2021**, *15*, 12687; b) S. Zhang, G. Ge, Y. Qin, W. Li, J. Dong, J. Mei, R. Ma, X. Zhang, J. Bai, C. Zhu, W. Zhang, D. Geng, *Mater. Today Bio* **2023**, *18*, 100508; c) D. Gao, Y. Zhang, D. T. Bowers, W. Liu, M. Ma, *APL Bioeng.* **2021**, *5*, 031503; d) Y. Xiong, Q. Feng, L. Lu, K. Zha, T. Yu, Z. Lin, Y. Hu, A. C. Panayi, V. Nosrati-Ziahmagi, X. Chu, L. Chen, M.-A. Shahbazi, B. Mi, G. Liu, *Adv. Funct. Mater.* **2023**, *33*, 2213066; e) A. Ko, C. Liao, *BMEMat* **2023**, *1*, e12037; f) K. Ghosal, D. Chakraborty, V. Roychowdhury, S. Ghosh, S. Dutta, *ACS Omega* **2022**, *7*, 43364; g) Y. Xu, Q. Hu, Z. Wei, Y. Ou, Y. Cao, H. Zhou, M. Wang, K. Yu, B. Liang,

- Biomater. Res.* **2023**, 27, 36; h) Q. Zeng, Z. Qi, G. Shi, M. Zhang, H. Haick, *ACS Nano* **2022**, 16, 1708.
- [2] a) H. Liu, Z. Li, Y. Zhao, Y. Feng, A. V. Zvyagin, J. Wang, X. Yang, B. Yang, Q. Lin, *ACS Appl. Mater. Interfaces* **2021**, 13, 23; b) C. Wang, M. Wang, T. Xu, X. Zhang, C. Lin, W. Gao, H. Xu, B. Lei, C. Mao, *Theranostics* **2019**, 9, 65.
- [3] a) W. Li, H. Chen, J. Cai, M. Wang, X. Zhou, L. Ren, *Adv. Funct. Mater.* **2023**, 49, 2303147; b) C. Hu, L. L. J. Cao, S. Zhang, Y. Wang, *Chem. Eng. J.* **2021**, 411, 128564; c) H. Chen, R. Cheng, X. Zhao, Y. Zhang, A. Tam, Y. Yan, H. Shen, Y. S. Zhang, J. Qi, Y. Feng, L. Liu, G. Pan, W. Cui, L. Deng, *NPG Asia Mater.* **2019**, 11, 3.
- [4] a) S. O. Blacklow, J. Li, B. R. Freedman, M. Zeidi, C. Chen, D. J. Mooney, *Sci. Adv.* **2019**, 5, eaaw3936; b) S. Liu, Q. Zhang, J. Yu, N. Shao, H. Lu, J. Guo, X. Qiu, D. Zhou, Y. Huang, *Adv. Health. Mater.* **2020**, 9, 2000198.
- [5] a) L. Han, X. Lu, K. Liu, K. Wang, L. Fang, L.-T. Weng, H. Zhang, Y. Tang, F. Ren, C. Zhao, G. Sun, R. Liang, Z. Li, *ACS Nano* **2017**, 11, 2561; b) W. Ma, X. Zhang, Y. Liu, L. Fan, J. Gan, W. Liu, Y. Zhao, L. Sun, *Adv. Sci.* **2022**, 9, 2103317.
- [6] L. Chen, Y. Chen, R. Zhang, Q. Yu, Y. Liu, Y. Li, *ACS Nano* **2022**, 16, 9929.
- [7] a) V. Leino, R. Airaksinen, M. Viluksela, K. Vähäkangas, *Toxicol. Rep.* **2021**, 8, 106; b) G. Liu, Y. Zhou, Z. Xu, Z. Bao, L. Zheng, J. Wu, *Chin. Chem. Lett.* **2023**, 34, 107705.
- [8] P. T. S. Kumar, V.-K. Laskmanan, T. V. Anilkumar, C. Ramya, P. Reshmi, A. G. Unnikrishnan, S. V. Nair, R. Jayakumar, *ACS Appl. Mater. Interfaces* **2012**, 4, 2618.
- [9] a) M. A. Matica, F. L. Aachmann, A. Tøndervik, H. Sletta, V. Ostafe, *Int. J. Mol. Sci.* **2019**, 20, 5889; b) G. Velazco, A. Gonzalez, R. Ortiz, *Avan. Biomed.* **2012**, 1, 38.
- [10] F. Abdollahimajd, M. R. Pourani, H. Mahdavi, H. Mirzadeh, S. Younespour, H. Moravvej, *Dermatol. Ther.* **2022**, 35, e15682.
- [11] M. S. Mirbagheri, S. Akhavan-Mahdavi, A. Hasan, M. S. Kharazmi, S. M. Jafari, *Carbohydr. Polym.* **2023**, 313, 120512.
- [12] H. Chijcheapaza-Flores, N. Tabary, F. Chai, M. Maton, J.-N. Staelens, F. Cazaux, C. Neut, F. Cazaux, C. Neut, B. Martel, N. Blanchemain, M. J. Garcia-Fernandez, *Gels* **2023**, 9, 292.
- [13] L. Jiang, X. Wu, Y. Wang, C. Liu, Y. Wu, J. Wang, N. Xu, Z. He, S. Wang, H. Zhang, X. Wang, X. Lu, Q. Tan, X. Sun, *Adv. Sci.* **2023**, 10, 2300339.
- [14] H. J. Forman, A. Bernardo, K. J. A. Davies, *Arch. Biochem. Biophys.* **2016**, 603, 48.
- [15] E. I. Oprita, A. Iosageanu, O. Craciunescu, *Gels* **2023**, 9, 867.
- [16] B. Hu, G. Mingzhu, K. O. Boakye-Yiadom, W. Ho, W. Yu, X. Xu, Z. Xue-Qing, *Bioact. Mater.* **2021**, 6, 4592.
- [17] Z. Zhang, C. Huang, S. Guan, L. Wang, H. Yin, J. Yin, J. Liu, J. Wu, *Biomater. Adv.* **2024**, 158, 213779.
- [18] T. W. Jung, H. S. Park, G. H. Choi, D. Kim, T. Lee, *Mol. Cells* **2017**, 40, 906.
- [19] H. Niu, Y. Guan, T. Zhong, L. Ma, M. Zayed, J. Guan, *NPJ Regen. Med.* **2023**, 8, 32.
- [20] B. S. H. Brem, O. Stojadinovic, M. Tomic-Canic, *Wound Repair Regen.* **2014**, 22, 569.
- [21] M. M. Martino, P. S. Briquez, E. Güç, F. Tortelli, W. W. Kilarski, S. Metzger, J. J. Rice, G. A. Kuhn, R. Müller, M. A. Swartz, J. A. Hubbell, *Science* **2014**, 343, 885.
- [22] H. Zhong, J. Huang, M. Luo, Y. Fang, X. Zeng, J. Wu, J. Du, *Nano Res.* **2023**, 16, 599.
- [23] a) N. C. Carrejo, A. N. Moore, T. L. Lopez Silva, D. G. Leach, I.-C. Li, D. R. Walker, J. D. Hartgerink, *ACS Biomater. Sci. Eng.* **2018**, 4, 1386; b) M. P. Lutolf, J. A. Hubbell, *Nat. Biotechnol.* **2005**, 23, 47.
- [24] K. Kim, Z. Siddiqui, A. M. Acevedo-Jake, A. Roy, M. Choudhury, J. Grasman, V. Kumar, *Macromol. Biosci.* **2022**, 22, e2200067.
- [25] a) J. I. Jones, T. T. Nguyen, Z. Peng, M. Chang, *Pharmaceuticals* **2019**, 12, 79; b) M. Hariono, S. H. Yuliani, E. P. Istyastono, F. D. O. Riswanto, C. F. Adhipandito, *Wound Med.* **2018**, 22, 1.
- [26] T. T. Nguyen, D. Ding, W. R. Wolter, R. L. Perez, M. M. Champion, K. V. Mahasenan, D. Heseck, M. Lee, V. A. Schroeder, J. I. Jones, E. Lastochkin, M. K. Rose, C. E. Peterson, M. A. Suckow, S. Mobashery, M. Chang, *J. Med. Chem.* **2018**, 61, 8825.
- [27] S. Chen, A. F. U. H. Saeed, Q. Liu, Q. Jiang, H. Xu, G. G. Xiao, L. Rao, Y. Duo, *Signal Transduct. Target Ther.* **2023**, 8, 207.
- [28] a) P.-C. Hao, T. Burnouf, C.-W. Chiang, P.-R. Jheng, S. Szunerits, J.-C. Yang, E.-Y. Chuang, *J. Nanobiotechnol.* **2023**, 21, 318; b) S. Liu, J. Yu, Q. Zhang, H. Lu, X. Qiu, D. Zhou, Y. Qi, Y. Huang, *Biomacromolecules* **2020**, 21, 3795.
- [29] J. Pajarinen, T. Lin, E. Gibon, Y. Kohno, M. Maruyama, K. Nathan, L. Lu, Z. Yao, S. B. Goodman, *Biomaterials* **2019**, 196, 80.
- [30] a) K. C. Rustad, V. W. Wong, M. Sorkin, J. P. Glotzbach, M. R. Major, J. Rajadas, M. T. Longaker, G. C. Gurtner, *Biomaterials* **2012**, 33, 80; b) H. Cho, M. R. Blatchley, E. J. Duh, S. Gerecht, *Adv. Drug Deliv. Rev.* **2019**, 146, 267; c) J.-N. Huang, H. Cao, K.-Y. Liang, L.-P. Cui, Y. Li, *World J. Diabetes* **2022**, 13, 949.
- [31] L. Zhao, L. Niu, H. Liang, H. Tan, C. Liu, F. Feiyan Zh, *ACS Appl. Mater. Interfaces* **2017**, 9, 43.
- [32] Y. Xiong, L. Chen, P. Liu, T. Yu, C. Lin, C. Yan, Y. Hu, W. Zhou, Y. Sun, A. C. Panayi, F. Cao, H. Xue, L. Hu, Z. Lin, X. Xie, X. Xiao, Q. Feng, B. Mi, G. Liu, *Small* **2021**, 18, 2104229.
- [33] K. E. Martin, M. D. Hunckler, E. Chee, J. D. Caplin, G. F. Barber, P. P. Kalelkar, R. S. Schneider, A. J. García, *Biomaterials* **2023**, 301, 122256.
- [34] a) V. Babaei, H. Afradi, H. Z. Gohardani, F. Nasser, M. Azarafza, S. Teimourian, *J. Wound Care* **2017**, 26, 784; b) M. He, T. Chen, Y. Lv, P. Song, B. Deng, X. Guo, S. Rui, J. Boey, D. G. Armstrong, Y. Ma, W. Deng, *Front. Bioeng. Biotechnol.* **2022**, 10, 993436.
- [35] A. Muacevic, J. R. Adler, *Cureus* **2022**, 14, e28292.
- [36] a) S. Jin, M. A. A. Newton, H. Cheng, Q. Zhang, W. Gao, Y. Zheng, Z. Lu, Z. Dai, J. Zhu, *Gels* **2023**, 9, 694; b) B. Mirani, E. Pagan, B. Currie, M. A. Siddiqui, R. Hosseinzadeh, P. Mostafalu, Y. S. Zhang, A. Ghahary, M. Akbari, *Adv. Health. Mater.* **2017**, 6, 1700718.
- [37] P. Mostafalu, A. Tamayol, R. Rahimi, M. Ochoa, A. Khalilpour, G. Kiaee, I. K. Yazdi, S. Bagherifard, M. R. Dokmeci, B. Ziaie, S. R. Sonkusale, A. Khademhosseini, *Small* **2018**, 14, 17035509.
- [38] Y. Gao, D. T. Nguyen, T. Yeo, S. B. Lim, W. X. Tan, L. E. Madden, L. Jin, J. Y. K. Long, F. A. B. Aloweni, Y. J. A. Liew, M. L. L. Tan, S. Y. Ang, S. Maniya, I. Abdelwahab, K. Ping Loh, C.-H. Chen, D. L. Becker, D. Leavesley, J. S. Ho, C. T. Lim, *Sci. Adv.* **2021**, 7, eabg9614.
- [39] V. Mishyn, M. Aslan, A. Hugo, T. Rodrigues, H. Happy, R. Sanyal, W. Knoll, F. Baudoux, V. Bouchiat, R. O. Bilyy, R. Boukherroub, A. Sanyal, S. Szunerits, *Sens. Diagn.* **2022**, 1, 739.
- [40] Q. Pang, D. Lou, S. Li, G. Wang, B. Qiao, S. Dong, L. Ma, C. Gao, Z. Wu, *Adv. Sci.* **2020**, 7, 1902673.
- [41] N. Tang, R. Zhang, Y. Zheng, J. Wang, K. M. X. Jiang, C. Zhou, R. Omar, W. Saliba, W. Wu, M. Yuan, D. Cui, H. Haick, *Adv. Mater.* **2022**, 34, 2106842.
- [42] a) Y. Yang, J. Huang, A. Zeng, X. Long, N. Yu, X. Wang, *Burns Trauma* **2024**, 12, tkad059; b) H. N. Wilkinson, A. R. Stafford, M. Rudden, N. D. C. Rocha, A. S. Kidd, S. Iveson, A. L. Bell, J. Hart, A. Duarte, J. Frieling, F. Janssen, C. Röhrig, B. de Rooij, P. F. Ekhardt, M. J. Hardman, *J. Invest. Dermatol.* **2024**, <https://doi.org/10.1016/j.jid.2024.01.018>.
- [43] T. Nakatsuji, T. H. Chen, S. Narala, K. A. Chun, A. M. Two, T. Yun, F. Shafiq, P. F. Kotel, A. Bouslimani, A. V. Melnik, H. Lati, J.-N. Kim, A. Lockhart, K. Artis, G. David, P. Taylor, J. Streib, P. C. Dorrestein, A. Grier, S. R. Gill, K. Zengler, T. R. Hata, D. Y. M. Leung, R. L. Gallo, *Sci. Transl. Med.* **2017**, 9, eaah4680.