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Review Article

Recent advances on thermosensitive hydrogels-mediated precision therapy

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ABSTRACT

Precision therapy has become the preferred choice attributed to the optimal drug concentration in target sites, increased therapeutic efficacy, and reduced adverse effects. Over the past few years, sprayable or injectable thermosensitive hydrogels have exhibited high therapeutic potential. These can be applied as cell-growing scaffolds or drug-releasing reservoirs by simply mixing in a free-flowing sol phase at room temperature. Inspired by their unique properties, thermosensitive hydrogels have been widely applied as drug delivery and treatment platforms for precision medicine. In this review, the state-of-the-art developments in thermosensitive hydrogels for precision therapy are investigated, which covers from the thermo-gelling mechanisms and main components to biomedical applications, including wound healing, anti-tumor activity, osteogenesis, and periodontal, sinonasal and ophthalmic diseases. The most promising applications and trends of thermosensitive hydrogels for precision therapy are also discussed in light of their unique features.

1. Introduction

Precision therapy provides targeted drug delivery at the site of the disease and avoids systemic side effects compared with systemic delivery techniques [1–3]. Many topical drug delivery systems, namely liposomes [4,5], micelles [6,7], hydrogels [8,9], nanoparticles [10,11], and microneedles [12,13], have made many attempts to enhance the local therapeutic efficacy in precision medicine. Among them, hydrogels have been recognized as the most common and convenient substrates in the biomedical field [14–18]. Hydrogels are three-dimensional (3D) crosslinked polymer networks that possess excellent qualities to absorb and swell in water or biological fluids without breaking the networks [19,20]. In the past decades, they have become one of the most promising carrier

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materials in biomedical fields because of their soft matter nature, excellent biocompatibility and biodegradability, and extremely hydrated nature similar to extracellular matrix (ECM) characteristics [21–25]. Crosslinking of traditional hydrogel focuses on chemical crosslinking networks to form permanent junctions in the polymer networks before treatment [26–30]. These types of hydrogels have severe limitations in practical application because they are not intelligent for responding to external or environmental stimuli, resulting in invasive, inconvenient, and painful administration for patients [31,32]. As medical needs continue to expand, "smart" hydrogels, which can sense various stimuli, including temperature, pH, pressure, light, ionic strength, and chemical and biological stimulations, have emerged showing immense potentialities in topical precision therapy [33–37].

Thermosensitive hydrogels, as a new category of smart materials, are particularly attractive and the most widely applied system due to many of their special features [38–42]. Compared to traditional hydrogels, simple temperature variations of difference outside and the human body can easily trigger thermosensitive hydrogels from well-solubilized solutions to gel state [43,44]. This enables the drug formulations to be exploited for a spray or injectable solution in a minimally invasive manner, and such hydrogel formulation can improve the local drug concentration and avoid systemic side effects caused by intravenous or trans-oral administration [45–47]. More importantly, the tunable characteristics of thermosensitive hydrogels make them versatile and capable of incorporating drugs or biotherapeutic molecules in the aqueous polymer solutions phase without requiring any denaturing cross-linking agent and additional organic solvents to induce gelation. Therefore, they are more biodegradable and biocompatible for application in health care [48,49]. In addition, they are superior to the conventional formulation in treating local diseases due to their fascinating properties, such as their low viscosity below body temperature, sustained release characteristics, minimal invasiveness, and fewer side effects [49–51]. Accordingly, these merits facilitate their exciting and extensive applications in the biomedical field, which can locally enhance drug delivery and improve drug bioavailability *via* the phase transition of thermosensitive hydrogels as ambient temperature changes.

Unlike previous reviews on hydrogel topics, this review mainly focuses on recent advances in thermosensitive hydrogel-mediated precision therapy and emphasizes the coverage of characteristics and temperature-responsive mechanism of thermosensitive polymers. Besides, it gives a systematical and well-organized description of recent advancements of thermosensitive hydrogels regarding diverse biomedical applications during the past decade, including wound healing, anti-tumors, osteogenesis, periodontitis, rhinosinusitis, and ophthalmic diseases, accentuating the active role played by thermosensitive hydrogels in precision therapy. In the end, the challenges and future perspectives of efficacious precision therapy using thermosensitive hydrogels as a platform are separately discussed in the conclusion.

2. Thermo-gelling mechanisms of thermosensitive hydrogels

With the development of biomaterials science, a variety of hydrogels has been synthesized by physical interactions and chemical cross-linking [52]. Within a physically crosslinked hydrogel, polymeric chains are reversible and hold together through molecular entanglement or secondary interactions *via* ionic crosslinks, π-π stacking, or hydrogen bonding interaction [53]. It makes it possible for physically crosslinked hydrogels to show particular advantages, including repairability, reversibility, and responsiveness in the absence of any crosslinking agent [54,55]. As a typical physically crosslinked hydrogel, thermosensitive hydrogels are usually divided into two types considering the source of composition materials (Table 1): synthetic polymers including poly (N-isopropylacrylamide) (PNIPAM), Poloxamer or Pluronic and polyethylene glycol (PEG)-polyester copolymer, etc., and natural biodegradable polymers, such as cellulose, chitosan (CS), and other naturally derived polymers. In numerous thermosensitive polymers, synthetic amphiphilic copolymers are surely the most studied thermosensitive polymers, which consist of the hydrophilic block and the hydrophobic block. As shown in Fig. 1A, A block denotes the hydrophilic block, which endows the amphiphilic copolymers with good biocompatibility and water solubility, while B and C blocks represent the hydrophobic blocks which provide hydrophobic drugs loading capacity [56].

Thermodynamically self-assembled micelle is favorable for amphiphilic copolymers in water, as amphiphilic block copolymers achieve critical micelle temperature and critical micelle concentration [57]. Generally, molecular weight, chain and block length, copolymer configurations, hydrophilic-lipophilic balance, and external additives may all affect micelle aggregation, then further influence the gelling mechanism and temperature-responsiveness of thermo-responsive hydrogels [58–61]. More specifically in gelling mechanism, aggregates forming is attributed to the break of hydrogen bonds and polymer contraction that is associated with the thermodynamical interactions between enthalpy, entropy, and temperature ($\Delta G = \Delta H - T\Delta S$) [62,63]. For example, the negative thermo-sensitive polymer hydrogels are free-flowing at lower temperatures while the entropy takes the front seat. Subsequently, as the ambient temperature goes up to the lower critical solution temperature (LCST) or higher, the hydrogen bonds break, and the micelles start to pack together tightly, which entraps water inside and causes sol-gel phase conversion. Therefore, the mechanisms of the gelation behavior of thermo-responsive hydrogel are the result of micellization, solution temperature, and micelle aggregation of thermos-gelling polymers [64–66]. The packing mechanism between different types of thermosensitive polymer micelles was approximately the same except for a slight difference. Three main existing packing mechanisms in negative thermosensitive copolymer micelles are outlined in Fig. 1B [56].

Table 1 – Mechanism and regulation of the typical thermosensitive polymers for suitable thermosensitivity and properties.

Polymers	CST (°C)	Characteristics	Adjustable way	Gelling mechanism	Ref
PNIPAM	~32	Non-degradable and most broadly studied	LCST : vary the side-chain length, crosslink with compatible copolymers, or mix with ionic liquids	Micellar corona collapse packing	[67–69]
Poloxamer	~37	Commercially available, fast dissolution rate, low mechanical strength and non-degradable	Viscosity and rigidity: change the concentration and composition	Individual micellar packing	[70–72]
PEG-polyester copolymer	~37	Biodegradable, but its acidic degradation products may cause an inflammation response	Gelling behaviors: MW, MWD, the structure and topology of the copolymer, the composition of the polyester	Short-chain diblock or ABA triblock copolymers: individual micellar packing; BAB, BAC triblock, and multiblock copolymers: inter-micellar bridged packing	[19,73-75]
CS	/	Adhesive, biodegradable and non-thermosensitive	Usually blend with β-GP	/	[76,77]
Cellulose derivatives	MC: ~80	The transition rate near physiological temperature is too slow	Gelation time↓: incorporate with other polymers	/	[78]
Gelatin	>40	Positive thermosensitive polymer and excessive transition temperature may denature some loaded biological agents	UCST↓: mix with other polymers	/	[79,80]

CST: critical solution temperature; PEG-polyester: polyethylene glycol-polyester; MC: methylcellulose; MW: molecular weight; MWD: molecular weight distribution; β-GP: sodium glycerophosphate; UCST: upper critical solution temperature.

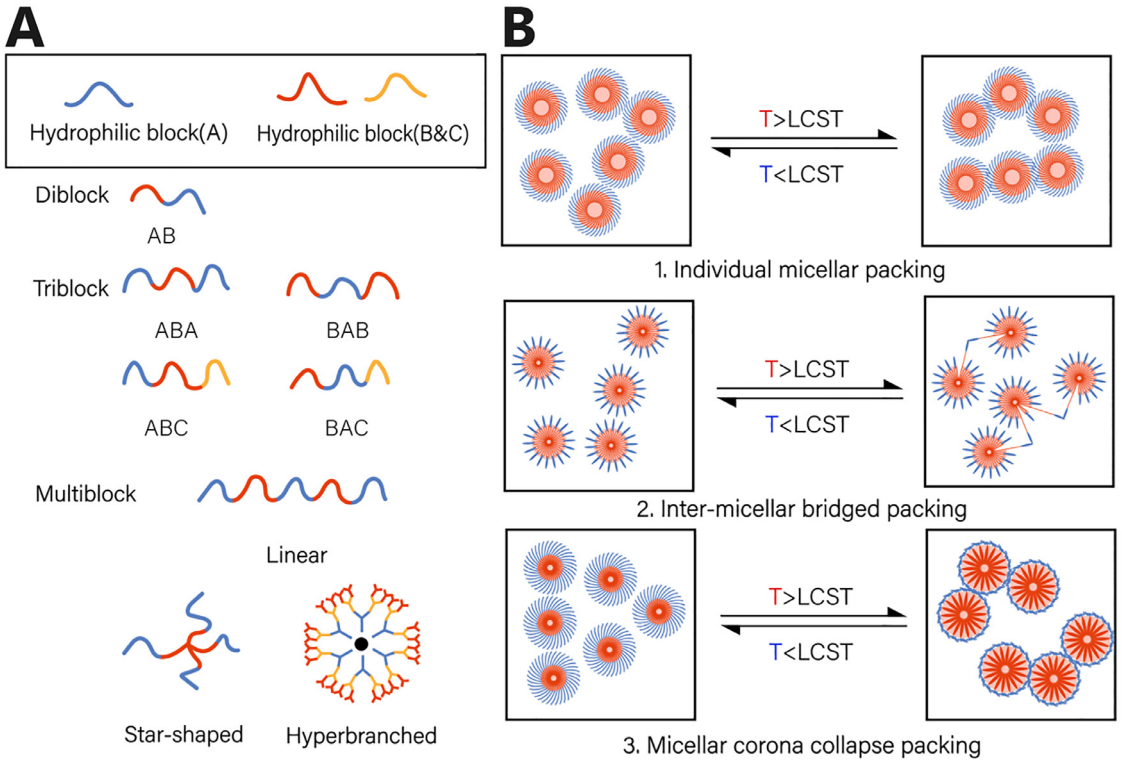

Fig. 1 – (A) Polymer configurations of thermosensitive copolymers. Synthetic amphiphilic copolymers can be categorized as diblock, triblock, and multiblock copolymers based on block number. The multiblock copolymers can be further classified into dendrimers, star-shaped, and linear block copolymers. (B) Three main mechanisms of micellization and gel formation in the aqueous solution.

3. Biomedical applications of thermosensitive hydrogels for precision therapy

Precision therapy is the preferred strategy due to its characteristics of avoiding first-pass metabolism and maintaining a high concentration of drugs in local lesions. What's more, precision therapy has many advantages in managing disease conditions and adverse reactions that could be reversed after drug withdrawal anytime [81,82]. Thermosensitive hydrogel, as a noninvasive mode of administration, has been regarded as one of the most promising precision treatment materials. Accordingly, the recent advances in biomedical applications of thermosensitive hydrogels will be outlined next [83]. The scope and organization of this review are exhibited in Fig. 2 and Table 2.

3.1. *Thermosensitive hydrogels for wound healing*

Wound healing is known to be a complicated and time-consuming process with various cell types and microenvironment conditions [84]. Plenty of dressings have been developed to accelerate wound healing, including foam [85], sponge [86], nanofibers [87], film [88] and bandages [89]. Compared with conventional wound dressings, thermosensitive hydrogels are the most hopeful candidates for wound dressings that can seal the ruptured skin or tissue in the sol state non-invasively completely at ambient temperature [90–93]. Most excitingly, not only can thermosensitive hydrogels fill the injured sites in the sol state non-invasively, but they also promote skin wound healing after transforming into gel at body temperature *via* maintaining a moist environment and protecting the wound from microbial invasion [41]. This section will illustrate the recent developments in the field of thermosensitive hydrogels for healing various types of wounds.

3.1.1. *Bacteria-infected wounds*

To gain the pharmacological and antibacterial activity, thermosensitive hydrogels usually need to be incorporated with various nanoparticles or bioactive moieties [94]. As shown in Fig. 3A, Liu et al. synthesized a sprayable adhesive for traumatic skin defects that could cover the irregular skin defect evenly and solidify rapidly [38]. This sprayable system was composed of Pluronic F127 (PF127) and a coordination complex of Zn and metformin (ZnMet), which could decrease reactive oxygen species (ROS) production and display excellent antibacterial activity. PEO-PPO-PEO (F127), as a common thermo-responsive hydrogel, is liquid below room temperature and can be sprayed by the nebulizer. The incorporation of ZnMet not only improved its mechanical strength but also endowed it with the pharmacological activity of angiogenesis, antimicrobial, collagen deposition, cell proliferation, and granulation tissue formation.

Among many thermo-responsive polymers, PNIPAM is a potential candidate for bioactive wound dressings because its phase transition temperature is approximate to physiological

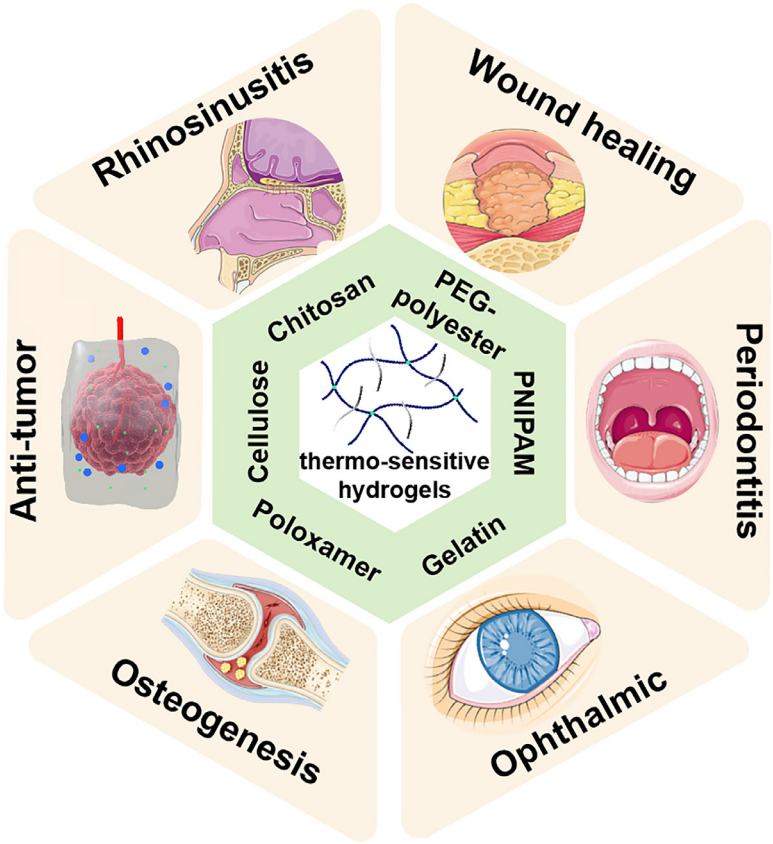

Fig. 2 – Schematic illustration of the thermosensitive hydrogels for biomedical applications.

Table 2 – Versatile developing methods and design strategies to develop thermosensitive hydrogels for precision therapy.

Polymer	Transition T (°C)	Developing methods	Main ingredient or drug	Design strategies or significant effects	Application	Ref.
F127	>20	Incorporating with various nanoparticles or bioactive moieties	A coordination complex of Zn and metformin	Sprayable; ZnMet decreased ROS production and displayed excellent antibacterial activity	Skin wounds	[38]
PEP	20	Copolymerized small content of hydrophobic nBA with PNIPAM to adjust the phase transition point below the body temperature;Modified PNIPAM with the strong synergistically coordination interactions between Ag@rGO nanosheets to enhance stability against decreasing temperature	Ag@rGO	The sol-gel irreversibility and excellent antibacterial activity	Skin wounds	[96]
GC	/	Incorporation of PDA nanoparticles	Ciprofloxacin-loaded PDA NPs	PTT; NIR-controlled release antibacterial drug	Skin wounds	[97]
P(NIPAM-AM)	49	Introduced a hydrophilic monomer acrylamide (AM) to copolymerize with NIPAM to tune the LCST of PNIPAM hydrogels into the therapeutic window (*i.e.*, 45–50 °C)	Colloidally stable AIE photothermal agent (denoted as MeO-TSI@F127)	PTT; regulates the photothermal equilibrium temperature	Skin wounds	[98]
PVP-PA	21.0 - 12.7	Neither PVP-PA nor laponite showed thermosensitivity in water upon heating, their nanocomposite system with a rational mixing ratio exhibited a temperature-induced sol-gel transition and formed a physical hydrogel with shear-thinning characteristics at physiological temperature	Laponite nano clay, iodine	Rapid hemostasis, antibacterial activity and good biological activity	Hemorrhagic wounds	[107]
NDP	15	Copolymerized small content of dopamine with PNIPAM to enhance adhesion	Fe_3O_4@rGO	Strong adhesion, rapid hemostasis, high magnetic hyperthermia	Hemorrhagic wounds	[108]
PLGA-PEG-PLGA	30.2	Incorporation of Nb_2C nanosheets	Nb_2C nanosheets	ROS-scavenging, PTT and hemostatic activity	Diabetic ulcer	[109]

(*continued on next page*)

Table 2 (*continued*)

Polymer	Transition T (°C)	Developing methods	Main ingredient or drug	Design strategies or significant effects	Application	Ref.
CS, β-GP, oHA	32	oHA could combine with CS *via* electrostatic interactions, optimizing the physical property of CS / β-GP gel, and shielding the excessively high positive charge of CS to further improve biocompatibility	HemSC-EVs	Soft, biocompatible, highly elastic deformable, and persistently release the EVs at a relatively constant rate	Diabetic ulcer	[110]
CS	37	Incorporation of B-TiO_{2-x} nanoparticles	Black TiO_{2-x} NPs	Excellent thermostability; simultaneous PTT and PDT; tissue regenerative activity	Cutaneous tumor	[117]
PLGA-PEG-PLGA	34.08	Incorporation of nHA nanoparticles	nHA, GM-CSF	Continuously release GM-CSF; boost and prolong anti-tumor immunity	Cutaneous tumor	[118]
F127, PPR, CMC	25	F127-CHO provided the primary network, thermosensitive and aldehyde group, PPR gave the fluorescence that can be monitored and amino group, CMC offered stability, biocompatibility and amino group, and the Schiff base reaction between the aldehyde group of FC and the amino group of PPR and CMC enhanced the self-healing ability to the hydrogel	Doxorubicin	Photoluminescent, injectability, good biocompatibility, pH-responsive degradation and drug release under a weak acidic condition due to the breaking of Schiff base bonds	Cutaneous tumor	[119]
PLGA-PEG-PLGA	18 - 25	/	Ti_6Al_4V implants, cisplatin	Increase the concentration of drugs at the target sites and load into 3D-printed implants conveniently	Osteosarcoma	[122]
PLEL	37	/	5-FU and DDP	Sustained drug release; combination therapy	Gastric cancer	[123]
CS, β-GP, gelatin	26.5	Incorporation of both drug-loaded PLGA NPs and free drugs	PLGA NPs loaded with BCNU and TMZ and free BCNU and TMZ	Combination therapy; ROS-sensitive release; avoid the blood-brain barrier	Glioma	[77]

(*continued on next page*)

Table 2 (*continued*)

Polymer	Transition T (°C)	Developing methods	Main ingredient or drug	Design strategies or significant effects	Application	Ref.
mPEG-*b*-PAla	9.5	mPEG-*b*-PAla was synthesized through the ROP of L-alanine N-carboxyanhydrides ($_L$-Ala-NCA) with amino-terminated mPEG (mPEG-NH_2) as a macroinitiator	Free REG and poly(l-lysine) nanogel encapsulated with LY	Combination therapy; achieve precisely sequential drug release	Rectal cancer	[114]
PEO-PPO-PEO	37	Carrying the rAAV-FLAG-hsox9 vector	rAAV	Deliver gene vectors in a controlled and spatiotemporally precise manner	Osteogenesis	[71]
PNIPAM	32	/	NiTi substrate	Inhibit bacterial adhesion and promot cell adhesion and proliferation after implantation	Osteogenesis	[127]
CS, β-GP, gelatin	37	The incorporation of gelatin could be applied to crosslink CS and β-GP through electrostatic interaction between cation and anion to minimize the gelation time	Aspirin and EPO	Continuously release drugs for at least 21 d	Periodontitis	[76]
F127, pyrophosphorylated F127	14	Mixing pyrophosphorylated F127 with regular F127 to improve the poor bone adhesion and mechanical properties	BIO	Exhibit stronger binding to hydroxyapatite; improve BIO's solubility in PF127 solution	Periodontitis	[72]
PNIPAM	34–35	Incorporation of PLGA microspheres	PLGA microspheres loaded with mometasone furoate	Continuously release drugs for at least 4 weeks	Rhinosinusitis	[131]
PNIPAM, PEG (2000 Da)	31.8–32.6	Prepared by aqueous free radical polymerization of N-isopropylacrylamide with the addition of PEG_{2000}	PLGA microspheres loaded with mometasone furoate	Could be stored in a ready-to-use format and provide greater ease of clinical translation	Rhinosinusitis	[132]
CS, β-GP, gelatin	15	Adjusting the different ratio of CS and gelatin	iPSC-MSCs exosomes	Continuously release iPSC-MSCs exosomes; prevent ECM deposition	Cornea regeneration	[135]

P(NIPAM-AM): poly (N-isopropyl acrylamide-co-acrylamide); PCLA: poly(e-caprolactone-co-lactide); PPR: polycitrate-polymine-rhodamine B polymer; CMC: Carboxymethyl chitosan; AIE: aggregation-induced emission;.

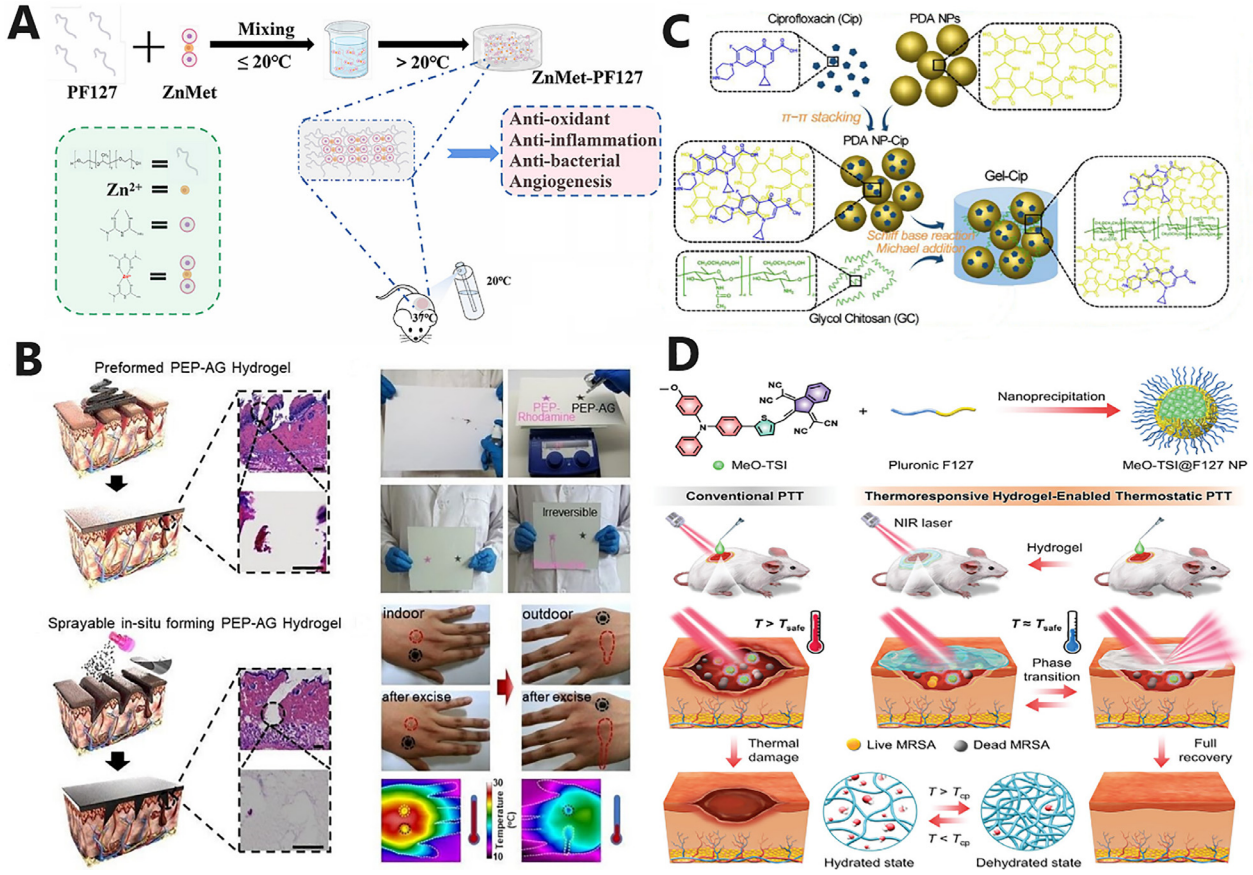

Fig. 3 – Thermosensitive hydrogels for bacteria-infected skin wounds. (A) A novel sprayable adhesive of ZnMet-PF127 hydrogel [38]. Copyright 2022 Elsevier. (B) Sprayable and irreversible *in-situ* forming PEP-AG hydrogel [96]. Copyright 2019 American Chemical Society. (C) The drug reservoir of PDA NP-Cip/GC hydrogel with NIR light-triggerable property [97]. Copyright 2019 Elsevier. (D) The thermo-responsive hydrogel-enabled thermostatic PTT with negligible thermal damages [98]. Copyright 2023 Wiley-VCH.

temperatures at 32 °C [95]. In another research, to adjust the LCST of PNIPAM-based hydrogels and endow them with antibacterial properties, He et al. loaded the Ag nanoparticle-decorated reduced graphene oxide nanosheets (Ag@rGO, which denoted AG) into a sprayable hydrogel composed of P(NIPAM$_{166}$-*co*-nBA$_9$)-PEG-P(NIPAM$_{166}$-*co*-nBA$_9$) copolymer (PEP) (Fig. 3B) [96]. This hydrogel exhibited the irreversible sol-gel-sol transition at low temperatures rather than reversible phase conversion as traditional thermo-responsive hydrogels. The in *vivo* experiments confirmed that this composite hydrogel with excellent antibacterial activity could promote the healing of a *methicillin-resistant Staphylococcus aureus* (MRSA) infectious skin defect. Therefore, the excellent free-flowing characteristic of thermosensitive hydrogels at ambient temperature could not only effectively fill the irregular wound defect but also significantly accelerate wound healing after incorporating active ingredients.

As an excellent delivery depot, thermosensitive hydrogels loaded with various antimicrobial agents for anti-infection therapy have been extensively reported [99–104]. To achieve a better antibacterial effect and slow down antibiotic resistance, a series of near-infrared (NIR) activatable drug release and NIR-responsive photothermal combined platforms were developed [97,103]. For instance, Wu et al. designed a drug delivery depot *via* mixing glycol chitosan (GC) and ciprofloxacin (Cip)-loaded polydopamine (PDA) nanoparticles (Fig. 3C) [97]. NIR irradiation could not only generate heat locally caused by PDA but also accelerated the ciprofloxacin release from thermo-sensitive hydrogels, both of which eliminated bacteria more effectively and inhibited infections more persistently in a synergistic way.

However, the hyperpyrexia generated by conventional photothermal therapy (PTT) inevitably causes damage to normal organs and skin. To maintain the photothermal equilibrium temperature below the preset safe threshold, Zhu et al. synthesized a thermo-responsive hydrogel-enabled thermostatic PTT system against bacteria-infected wounds (Fig. 3D) [98]. Upon NIR irradiation, the heat generation triggered by PTT nanoparticles was transferred to PNIPAM-based hydrogels, which could undergo a phase transition rapidly to form an opaque white gel for blocking NIR penetration. These reversible sol-gel transition properties could regulate the photothermal equilibrium temperature to the phase-transition point of the thermo-responsive hydrogel, which accelerated wound healing through efficient bacterial clearance with no evident thermal damage. This smart PTT

platform opened up a new avenue against bacterial skin infections.

3.1.2. *Hemorrhagic wounds*

Hemorrhagic wounds are responsible for most trauma-related mortality, especially on the battlefield. Among various hemostatic materials for hemorrhagic wounds, thermosensitive hydrogels are considered to be one of the most promising biomaterials [104]. Thermosensitive hydrogels can be quickly distributed on the wound surface and achieve temperature-dependent hemostasis owing to their phase transition [105]. Once the hemorrhage has been stabilized, the gel can be easily removed by cold water without any rebleeding or leaving any residues. This injectable functionality also enables thermosensitive hydrogels to show promising application and clinical potential for minimally invasive hemostasis applications, *e.g.*, organ bleeding [106]. Recently, a simple yet effective method using amphiphilic poly (*N*-vinyl pyrrolidone)-*b*-poly ($_{D,\ L}$-alanine) (PVP-PA) diblock copolymers and laponite nano-clay to produce composite hemostatic hydrogel was reported. The introduced PVP-PA and laponite in water could self-assemble to nanocomposite aggregation driven by electrostatic interactions and hydrogen bonding, and a temperature-triggered phase transition was attributed to the assembly aggregation coupled with the partial conformation transformation of PVP and PA segments (Fig. 4A) [107]. In the SD rats model of heart puncture and liver resection, the bioactive nanocomposite hydrogel could accelerate clot formation and achieve rapid hemostasis within 10 s.

Similarly, another thermosensitive hydrogel has been built by a triblock polymer poly (NIPAM-*co*-DOPA)-PEG-poly (NIPAM-*co*-DOPA) (NDP) matrix which underwent *in situ* gelation being triggered by the body temperature (Fig. 4B) [108]. Reduced graphene oxide nanosheets decorated with Fe_3O_4 nanoparticles (Fe_3O_4@rGO) have been introduced into the hydrogel matrix, which enhanced the hemostatic ability *via* blood coagulation. In the design, the thermosensitive preparties of hydrogel come from the PNIPAM on the polymer chain segment, and the good blood coagulation ability contributes to stopping bleeding during hepatectomy. Taken together, the various capabilities of thermosensitive hydrogels, such as syringeability, rapid hemostasis, and tissue repair, may contribute to meeting the needs of all stages of wound healing.

3.1.3. *Diabetic wounds*

Diabetes complications, particularly diabetic ulcers (DU), are a major clinical challenge in the life quality of patients, due to the complex chronic nonhealing wounds, hypoxia, poor angiogenesis, persistent infection, and long-term inflammation [111,112]. To overcome these limitations and satisfy the tunable functions, Chen suggested an injectable niobium carbide (Nb_2C)-based hydrogel (Nb_2C@Gel) with antioxidative and anti-infection properties, which was implanted Nb_2C nanosheets into poly(lactic-co-glycolic acid) poly (ethylene glycol) poly(lactic-co-glycolic acid) (PLGA-PEG-PLGA) triblock copolymers (Fig. 5A) [109]. This composite hydrogel exhibited good biocompatibility and could efficiently eliminate ROS in DU. In addition, Nb_2C@Gel was also a NIR-activatable hyperthermia-assisted antibacterial platform against both *Escherichia coli* and *Staphylococcus aureus*. Therefore, the Nb_2C@Gel system appeared to be an effective and promising strategy for DU, as it protected cells from ROS damage and activated the photothermal effect under NIR irradiation to eradicate bacteria simultaneously.

In addition, treatment for microcirculation reconstruction was regarded as a key solution in DU repair. In another

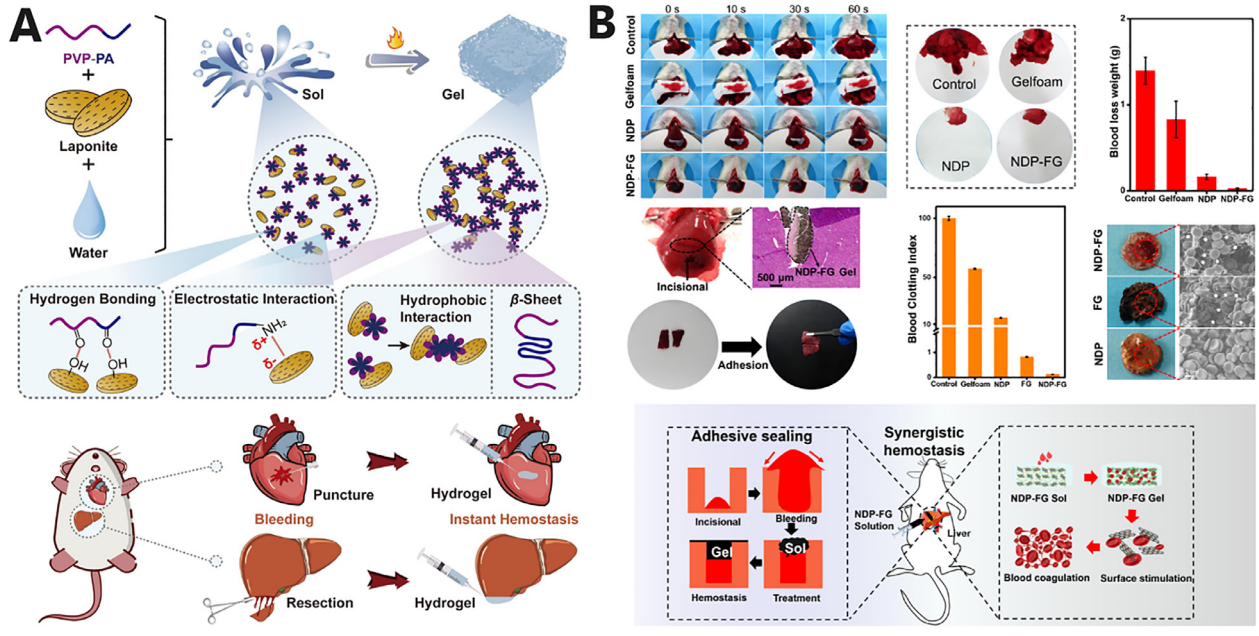

Fig. 4 – Thermosensitive hydrogels for hemorrhagic wounds. (a) Schematic of the fabrication and temperature-induced gelation mechanism of the nanocomposite hydrogel [107]. Copyright 2023 Elsevier. (b) Hemostasis behaviors of NDP-FG hydrogel [108]. Copyright 2022 American Chemical Society.

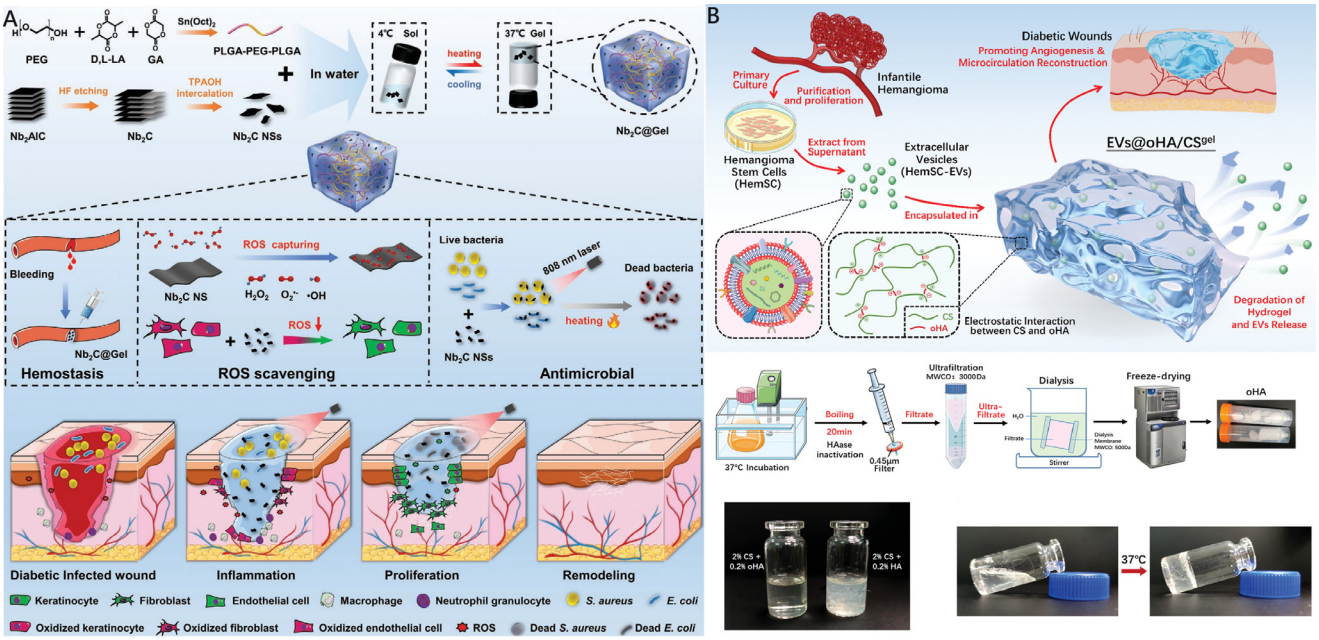

Fig. 5 – Thermosensitive hydrogels for diabetic wounds. (A) Schematic illustration of construction and application of Nb_2C-based hydrogel [109]. Copyright 2022 Wiley-VCH. (B) The preparation of EVs@oHA/CS hydrogel and the verification of angiogenic effect [110]. Copyright 2023 Wiley-VCH.

recent report, extracellular vesicles (EVs) derived from hemangioma stem cells (HemSC) were considered for strong angiogenic activity. In order to develop a perfect delivery carrier for HemSC-EVs, Sha et al. designed a thermosensitive hydrogel consisting of CS and modified with hyaluronic oligosaccharides (oHA) (Fig. 5B) [110]. oHA could cross-link with CS *via* electrostatic interaction, making CS hydrogel softer and highly elastic deformable and having an angiogenic effect to some extent. The EVs@oHA/CS hydrogel system could persistently deliver EVs for microcirculation reconstruction in DU, which could maintain the shape and structure of EVs. It is worth noting that the common strategy of introducing bioactive nanoparticles or active ingredients has enabled the development of a variety of thermosensitive hydrogels with unique functionalities and bioactivities [113].

3.2. *Thermosensitive hydrogels for anti-tumor applications*

Over recent decades, cancer has been represented as one of the leading factors of mortality and morbidity. Precision therapy is the most promising one among numerous treatment options, as it not only avoids chemotherapeutic toxicity in the systemic circulation but also lessens the required amount to maintain therapeutic levels. However, traditional delivery systems for precision drug release suffered from low bioavailability and poor local retention [44]. By virtue of their advantages in minimally invasive or non-invasive drug delivery, thermosensitive hydrogels have been deemed as one of the most promising biomaterials for tumor treatment that can achieve adequate local drug concentration by intra-tumoral injection, sustained drug release, and minimal systemic side-effects [113,114]. Next, a more exhaustive description of thermosensitive hydrogel for anti-tumor application is reviewed below.

3.2.1. *Superficial tumors*

Superficial tumors, such as malignant melanoma and breast cancer, are the most commonly encountered cancers and the mainstay of treatment is surgical intervention *via* removing both superficial tumors and the surrounding skin tissues. However, the potential risks of incomplete surgical resection, full-thickness cutaneous defects following surgery, wound infection and chronic inflammatory wound almost inevitably induce tumor recurrence and poor wound healing [115,116]. To heal the skin wounds and eliminate possible residual cutaneous tumor cells, Wang et al. exploited a defective black nano-titania (TiO_2)/CS hydrogel (BT-CTS) equipped with effective inhibition of melanoma reoccurrence and simultaneous tissue reconstructive ability (Fig. 6A) [117]. It was found that nano-sized black titania (B-TiO_{2-x}) nanoparticles reduced by Mg endowed the CS hydrogels with simultaneous PTT and photodynamic therapy (PDT). After peritumoral injection, these hybrid formulations could rapidly increase and exceed 50 °C and simultaneously induce the generation of ROS irradiated by NIR to halt the growth of local tumor cells. Moreover, the Mg^{2+} released from BT-CTS hydrogels not only enhanced the migration and adhesion of normal skin cells but also significantly facilitated skin wound closure. Therefore, a thermosensitive hydrogel with excellent thermostability, easy injectability, and simultaneous PTT/PDT efficacy offers an attractive strategy against cutaneous tumor-induced wounds.

Due to its reversible sol-gel phase transition and degradation properties, the thermosensitive hydrogel is an attractive sustained-release drug delivery system that can potentiate the benefits afforded for local and abscopal effects

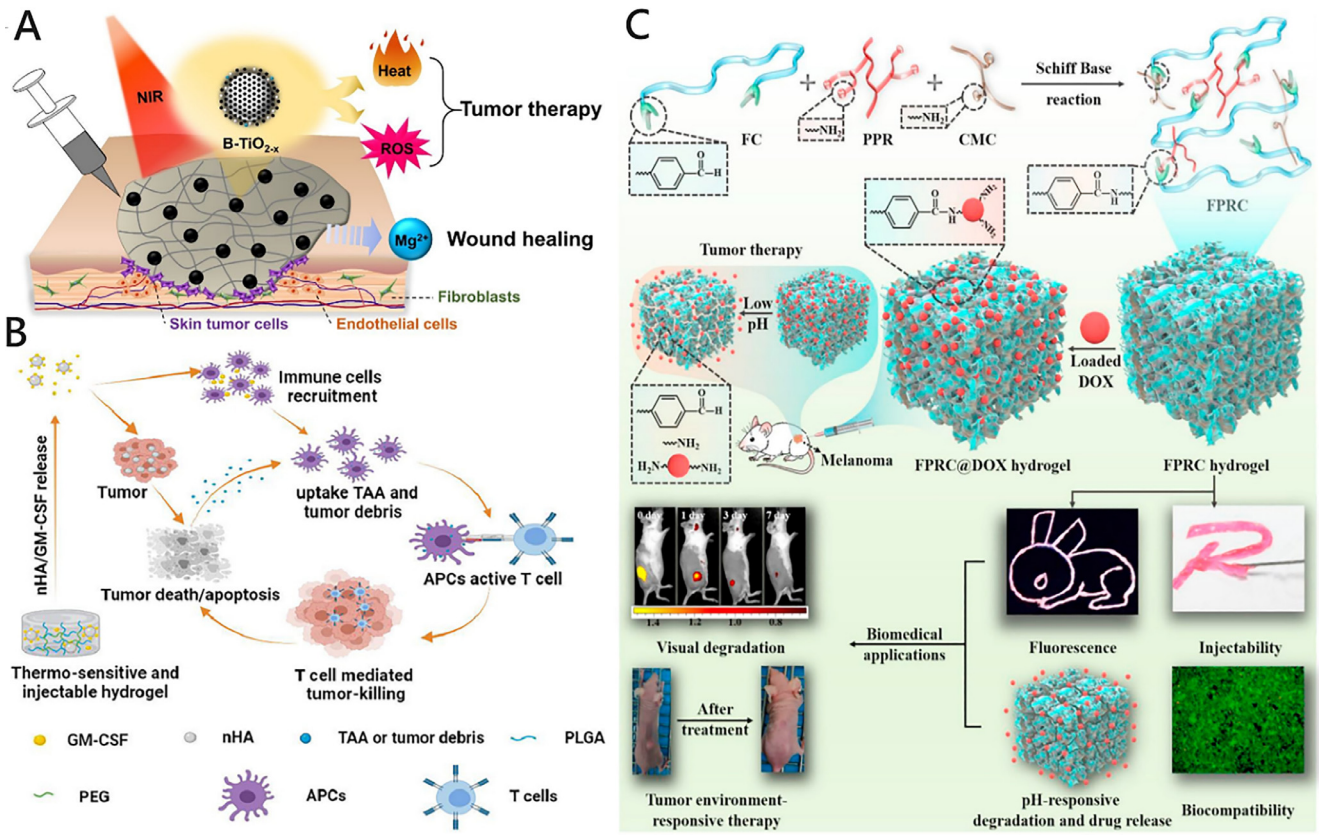

Fig. 6 – Thermosensitive hydrogels for superficial tumors. (A) BT-CTS thermogels with simultaneous PTT/PDT efficacy as well as tissue regenerative activity [117]. Copyright 2019 American Chemical Society. (B) nHA/GM-CSF-loaded hydrogel evoking a boosted and prolonged anti-tumor immunity [118]. Copyright 2022 Elsevier. (C) The synthesis process and application of multifunctional F127-CHO (FC)-PPR-CMC hybrid hydrogel system (FPRC hydrogel) [119]. Copyright 2020 Elsevier.

of cancer immunotherapy [47]. In another research, a delivery system of co-encapsulation of both nano-hydroxyapatite (nHA) and granulocyte-macrophage colony-stimulating factor (GM-CSF) into a PLGA-PEG-PLGA hydrogel was developed [118], as shown in Fig. 6B. This formulation showed continuous GM-CSF liberation instead of the burst release at the tumor site which may possibly result from the protein absorption capacity of nHA, which was crucial for the enhancement of the prolonged anti-tumor immunity effect. The results presented that the nHA/GM-CSF hydrogel displayed greater potency to improve immune response due to the synergistic effects of GM-CSF and nHA.

The strategy of tracking and quantifying the degradation of hydrogels by fluorescence imaging has gained large interest in recent years. Nevertheless, the further application of the current fabricated fluorescent hydrogels in the biomedical field has been severely impeded due to the lack of unique properties, for example, non-injectability, drug burst release, and microenvironment-responsive degradation. Wang and Lei's group reported an injectable hybrid hydrogel system based on F127 for efficient melanoma therapy, which possessed multifunctional properties such as thermosensitive, fluorescence ability, visual biodegradation tracking, and typical pH-responsive doxorubicin (DOX) release/hydrogel degradation (Fig. 6C) [119]. The fluorescent scaffold covalently immobilized to F127 hydrogels could be monitored and tracked to evaluate the degradation of the hydrogel *in vivo*, owing to its strong red fluorescence, good photostability, and tissue penetration. In summary, a thermosensitive hydrogel is an ideal carrier for cancer precise therapy, which can release drugs continuously, avoid systemic toxicity, and improve the local and abscopal effects of immunotherapy [120,121].

3.2.2. *Deep tumors*

In addition to cutaneous tumors, the most common are various deep tumors. Osteosarcoma is considered to be the most common malignant bone tumor. Surgical resection combined with perioperative neoadjuvant chemotherapy is the standard treatment for anti-osteosarcoma. However, there are many intrinsic disadvantages of traditional chemotherapy administered intravenously. The drug concentration in the postoperative area, limited by serious systemic adverse effects, is too low to inhibit tumor metastasis and recurrence. Therefore, to develop a functional implant for both bone substitution and drug release depot, Liu et al. constructed 3D-printed titanium alloy (Ti_6Al_4V) implants loaded with cisplatin using a PLGA-PEG-PLGA copolymer. The PLGA-PEG-PLGA copolymer was an ideal scaffold to deliver higher cisplatin concentrations and avoid systemic adverse effects

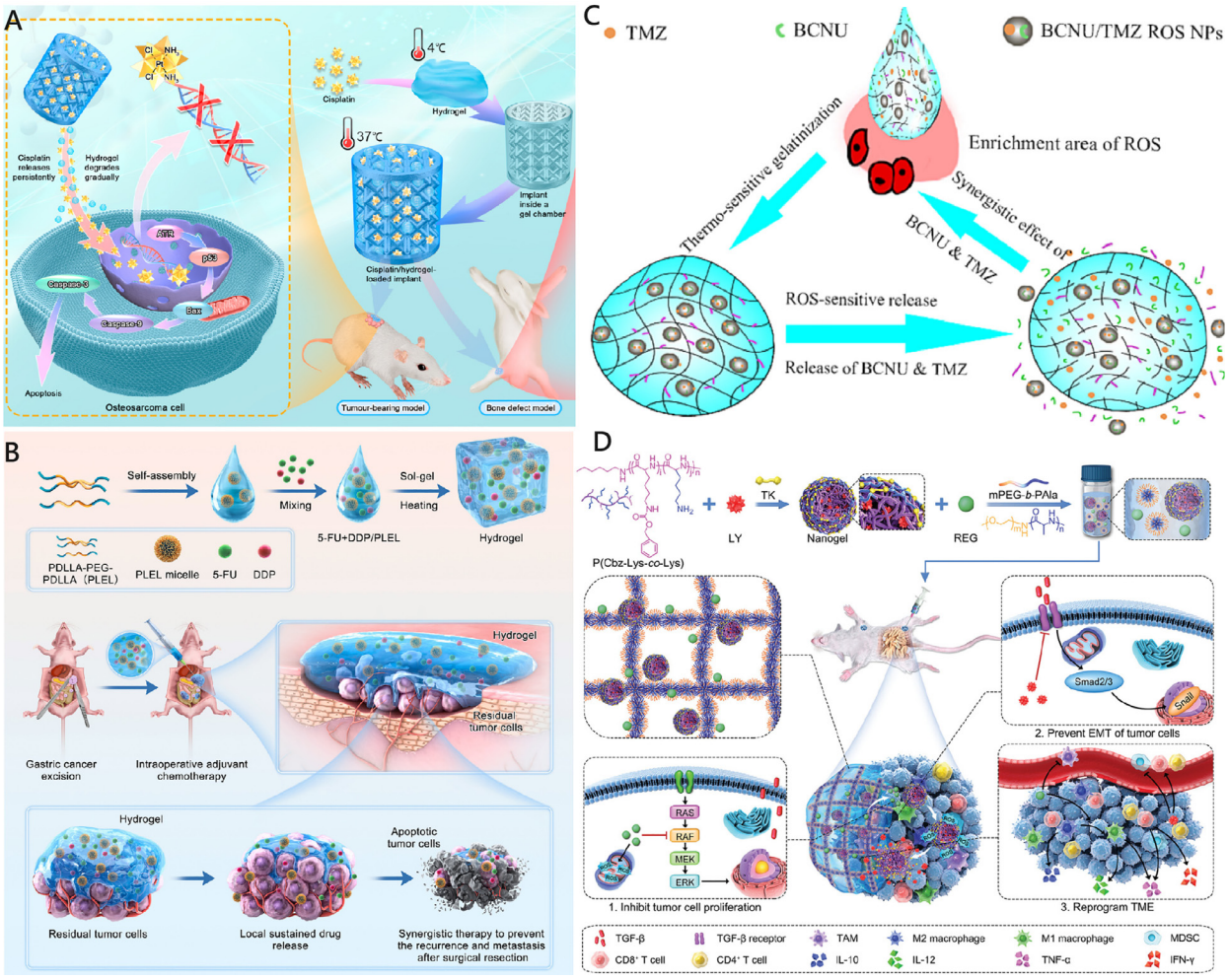

Fig. 7 – Thermosensitive hydrogels for deep tumors. (A) Cisplatin/hydrogel-loaded 3D-printed Ti_6Al_4V implants for osteosarcoma [122]. Copyright 2021 Elsevier. (B) 5-FU + DDP/PLEL hydrogel for intraoperative synergistic combination chemotherapy of gastric cancer [123]. Copyright 2023 Elsevier. (C) BCNU-TMZ&ROS NPs@Gel for post-surgical glioma recurrence [77]. Copyright 2022 Elsevier. (D) Gel/(REG+NG/LY) for colorectal tumor [114]. Copyright 2022 Wiley-VCH.

(Fig. 7A) [122]. The Ti_6Al_4V implants used in conjunction improved the mechanical strength of thermosensitive hydrogels, which were conducive to treating osteosarcoma-caused bone defects. This strategy combining thermosensitive hydrogels with metallic implants provided a new approach for the precision therapy of osteosarcoma.

In order to obtain better anti-tumor efficacy, combination therapy using different chemotherapeutic drugs has increasingly become a trend. In a study for intraoperative adjuvant combination chemotherapy of gastric cancer, Qian et al. designed a cisplatinum (DDP) and 5-fluorouracil (5-FU) local sustained co-delivery system based on a PDLLA-PEG-PDLLA (PLEL) hydrogels (Fig. 7B) [123]. Compared with a commercial fluorouracil implant, PLEL hydrogel could be easily distributed evenly at the surgical wound and then serve as a chemotherapeutic agent reservoir on site, owing to its sensitive sol-gel transition property. Similarly, in order to inhibit post-surgical glioma recurrence, a dual-sensitive drug release system co-loaded with bis(2-chloroethyl) nitrosourea (BCNU) and temozolomide (TMZ) was developed to prolong and enhance the synergistically therapeutic effect of drugs (Fig. 7C) [77]. In this study, hydrogel prepared by CS, gelatin, and β-GP was loaded with both drug-loaded ROS-sensitive PLGA nanoparticles and free drugs. The dual-drugs loaded hydrogel system overcame the blood-brain barrier and yielded sustained drug release mainly because of the bio-adhesive and injectable properties of CS thermosensitive hydrogel.

However, the therapeutic effects of synergistic therapy are usually less than expected in clinical applications, hindered by the release sequence and spatiotemporal distribution of drugs. Therefore, it is essential to control the release of component drugs *in vivo* spatiotemporally and sequentially. Sun et al. developed a tumor microenvironments-adapted hydrogel based on methoxy poly(ethylene glycol)-block-poly($_L$-alanine) (mPEG-*b*-PAla) hydrogel and a ROS-responsive nanogel for releasing two drugs sequentially against orthotopic colorectal tumors (Fig. 7D) [114]. After administration *in situ*, free regorafenib (REG) released preferentially from hydrogels and gradually promoted ROS generation, then induced the subsequent release of TGF-β

inhibitor (LY3200882, LY), which was encapsulated in a ROS-responsive nanogel. Compared with simultaneous delivery, the sequential release of REG and LY enhanced the anti-tumor immune responses and the effect of combination therapy *in vivo*. These studies all demonstrated that thermosensitive hydrogel as a synergistic chemo-drugs delivery system had great potential in precision therapy for deep tumors.

3.3. *Thermosensitive hydrogels for osteogenesis*

Cartilage defect has a limited ability for self-repair because it is uniquely avascular. Thermosensitive hydrogels are ideal preparations for bone and cartilage repair as they are well 3D porous scaffolds that support the proliferation, attachment, and 3D spatial organization of the cell population. They can be injected directely or through minimally invasive arthroscopic interventions without invasive surgery [75,124-126]. For example, the poloxamers hydrogel encapsulating recombinant adeno-associated viral (rAAV) vectors was reported first time for cartilage repair *in vivo* (Fig. 8A) [71]. Poloxamer is an ABA-type triblock copolymer, which is particularly attractive material for biomaterial-guided gene vector delivery in a consistent and minimally invasive way. The data in a clinically relevant minipig model supported that thermosensitive hydrogels were capable of controlled release of a therapeutic rAAV vector overexpressing the chondrogenic sox9 transcription factor, and the early bone loss of subchondral bone plate reversed postoperatively.

Titanium-based implants have been used in orthopedic disorders for many years due to their excellent biocompatibility, corrosion resistance, and mechanical properties. Unfortunately, it is difficult to satisfy both the preferable antibacterial property and osteogenesis for metallic implants. In this study, to decrease bacterial adhesion and increase cell adhesion and proliferation simultaneously, porous structures grafting with the PNIPAM-based hydrogel on a nitinol (NiTi) substrate were fabricated (Fig. 8B) [127]. At 25 °C, both bacteria and cells were repelled on the substrate surface owing to the hydration layer of the PNIPAM. Instead, when the temperature rose to 37 °C, the hydration layer of the PNIPAM hydrogel disappeared. Whereas the nanoporous structures retained water in the pores, which resulted in a high-hydration-rate sample surface and the reduction of bacterial adhesion sites. Meanwhile, the adhesion of larger cells was not affected by the porous structure. The results *in vivo* demonstrated that the PNIPAM hydrogel slightly reduced the surface modulus and the hardness of the porous NiTi sample, which enhanced osteogenesis. This work also provided additional ideas for the application of thermosensitive hydrogels in orthopedic implantation.

3.4. *Thermosensitive hydrogels for periodontitis*

One of the non-reversible and major destructive hallmarks of periodontitis is alveolar bone resorption. To terminate periodontal bone loss, it is essential to modulate inflammation and intervene in bone resorption simultaneously in periodontal disease [128]. Utilizing this strategy, an injectable hydrogel prepared by CS, gelatin, and β-GP was applied to continuously release aspirin and erythropoietin (EPO), respectively (Fig. 9) [76]. Clinically, repeated administration is required for aspirin and EPO due to their short half-lives. In this work, the releasing profile showed that the mixed hydrogels loaded with aspirin/EPO exhibited no toxicity and continued a sustained release till the 21st d. More importantly, compared with EPO, aspirin

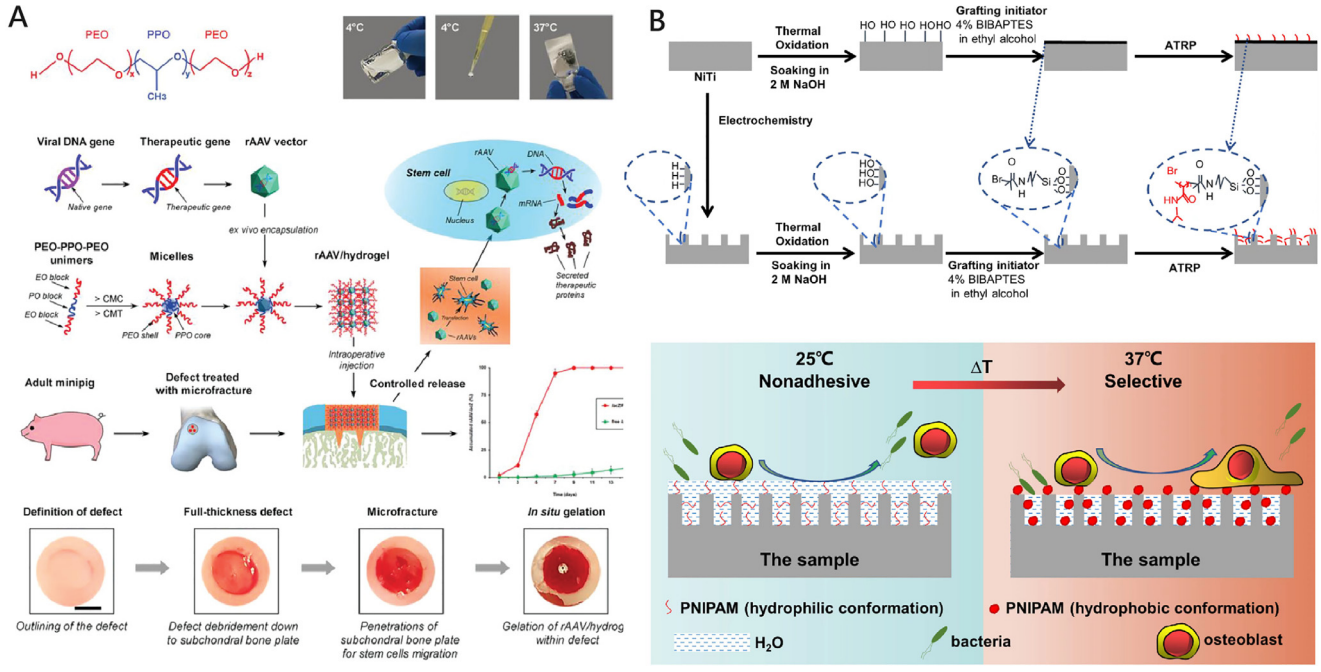

Fig. 8 – Thermosensitive hydrogels for osteogenesis. (A) sox9/hydrogel for a controlled *in situ* release of rAAV for cartilage defects [71]. Copyright 2020 Wiley-VCH. (B) Loading of the thermosensitive PNIPAM hydrogel on the NiTi substrate [127]. Copyright 2022 Elsevier.

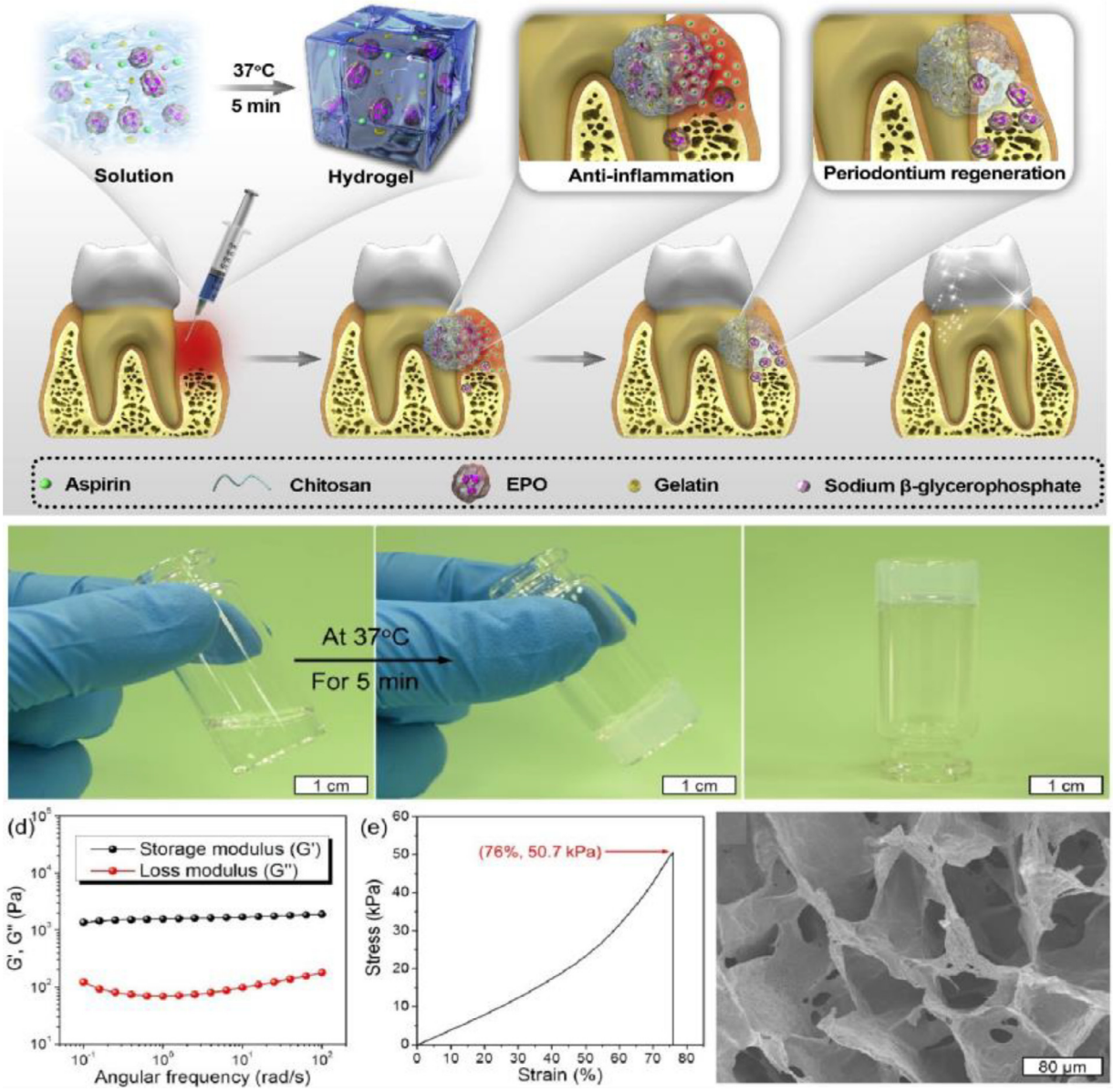

Fig. 9 – Thermosensitive hydrogels for periodontitis. An injectable CS/β-GP/gelatin hydrogel with pharmacological effects of anti-inflammation and tissue regeneration [76]. Copyright 2019 Elsevier.

demonstrated a faster release rate in the early stage, contributing to providing an appropriate microenvironment for bone regeneration by EPO and synergistically achieving anti-inflammation and periodontium regeneration.

In another study, glycogen synthase kinase 3β inhibitor (BIO), as an excellent anti-inflammatory and osteogenic drug, was loaded into PF127 consisting of the mixture of regular F127 and pyrophosphorylated F127 [72]. Hydrogel formulations dramatically improved the BIO's solubility and adhesion to hydroxyapatite compared to regular F127 hydrogel, leading to the retention time protraction and the sustained effective dose of BIO. After being administrated with hydrogel formulations weekly, periodontal inflammation and regeneration of the alveolar bone were significantly improved in the rat model with periodontitis. Altogether, the above results suggested that thermo-responsive hydrogel was an effective local drug carrier system for better precision management of periodontitis due to its natural adhesive performance and sustained drug release.

3.5. *Thermosensitive hydrogels for rhinosinusitis*

Chronic rhinosinusitis (CRS) is a complex heterogeneous disease characterized by sinonasal inflammation, and long-term steroid administration is required to prevent disease recurrence [129,130]. A promising delivery system called TEMPS (thermogel extended-release microsphere-based delivery to the paranasal sinuses) that could provide sustained steroid release for sinonasal mucosa inflammation has been designed by Steven R. Little group [131]. The

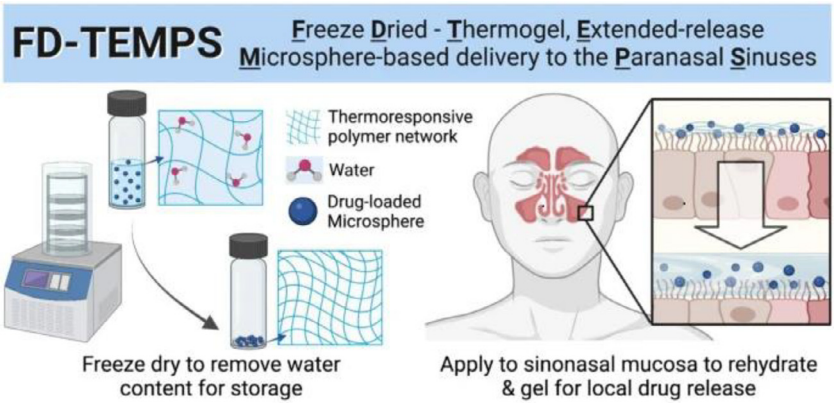

Fig. 10 – Thermosensitive hydrogels for rhinosinusitis. Swelling and gelation of freeze-dried FD-TEMPS formulations. Reproduced with permission [132]. Copyright 2021, Springer Nature.

combination of controlled-release microspheres with thermosensitive hydrogels could encapsulate corticosteroids and conform to the sinonasal mucosa by mimicking the native mucus layer for localized delivery to the sinuses. Specifically, the corticosteroid mometasone furoate was released for 4 weeks from PLGA microspheres embedded in a PNIPAM-based hydrogel. *In vivo* rabbit model of CRS, the composite hydrogel system underwent a rapid sol-to-gel transition when contacted with the sinonasal epithelium and effectively reduced sinonasal inflammation. Subsequently, to enhance shelf stability and uniformity of inhalation through the sinonasal mucosa, a freeze-dried sustained release system (FD-TEMPS) was further developed (Fig. 10) [132]. When contacting the mucus layer that consists of ~ 95 % water (w/w), the dried TEMPs could rehydrate and then gel at physiological temperature. Therefore, thermosensitive hydrogels provide flexibility for encapsulating drugs in a reversible and conforming system for topical precision delivery to the sinuses.

3.6. *Thermosensitive hydrogels for ophthalmic diseases*

Considering the eye as a relatively independent organ, topical dosing of ophthalmic drugs is the most preferential and widely accepted route for various anterior segment eye diseases attributed to its convenient features and non-invasiveness. However, conventional eye preparations suffer from multiple physiological protective barriers, including lachrymation, blinking, and nasolacrimal drainage, which result in extremely low bioavailability (< 5 %) and bring the development of local drug delivery great challenges [133,134]. Fortunately, thermosensitive *in situ* hydrogels can enhance drug bioavailability by avoiding the above-mentioned issues that can not only be administered as a liquid eye drop but also increase the drug's local retention [135].

Yao et al. developed an induced pluripotent stem cell-derived mesenchymal stem cells (iPSC-MSCs)-induced exosome hydrogel system based on thermosensitive CS hydrogels for corneal repair (Fig. 11) [135]. The exosome (iPSC-MSCs) could downregulate messenger RNA (mRNA) expression in corneal stroma coding for the collagens related to scar formation. The hydrogel group *in vivo* displayed that a more regular arrangement that appeared in the reconstructed epithelium closely resembles the healthy tissue, while an irregularly arranged physiologic and increased layers of cells were exhibited in the control wound group after surgery. More importantly, nano hydrogel as an ocular dressing loaded with drugs for ophthalmic diseases could be instilled easily like eye drops but form a transparent dressing on contact with the cornea. The eye preparations promoted transocular penetration, and in-situ gel prolonged the precorneal residence time to decrease drug loss [136]. The above studies indicated that thermosensitive hydrogels could drop off instilled frequency, which may result from prolonging retention and improving the ocular bioavailability of drugs at the desired site. Overall, thermosensitive hydrogels are highly promising biomaterials for topical precision therapy of various corneal diseases.

In addition, thermosensitive hydrogels have many applications in other fields, such as bioimaging [137,138], vasospasm [41], ulcerative colitis [70], iron overload [51], nerve regeneration [139] and spinal cord injury [49], etc. This review mainly emphasized their potential biomedical application in precision therapy for common diseases, so a detailed discussion will not be highlighted here.

4. Limitations and challenges

As smart hydrogels, thermosensitive hydrogels have many fascinating properties, including unique temperature-induced reversible sol-gel transition without additional organic solvents, desirable spatial and temporal control, and improved drug bioavailability. These inherent properties together with their excellent biocompatibility render thermosensitive hydrogels to be an ideal biomaterial for the design and construction of novel versatile platforms [14,19]. However, few thermosensitive hydrogels can be used directly for biological applications whose tunable parameters and pharmacological effects usually need to

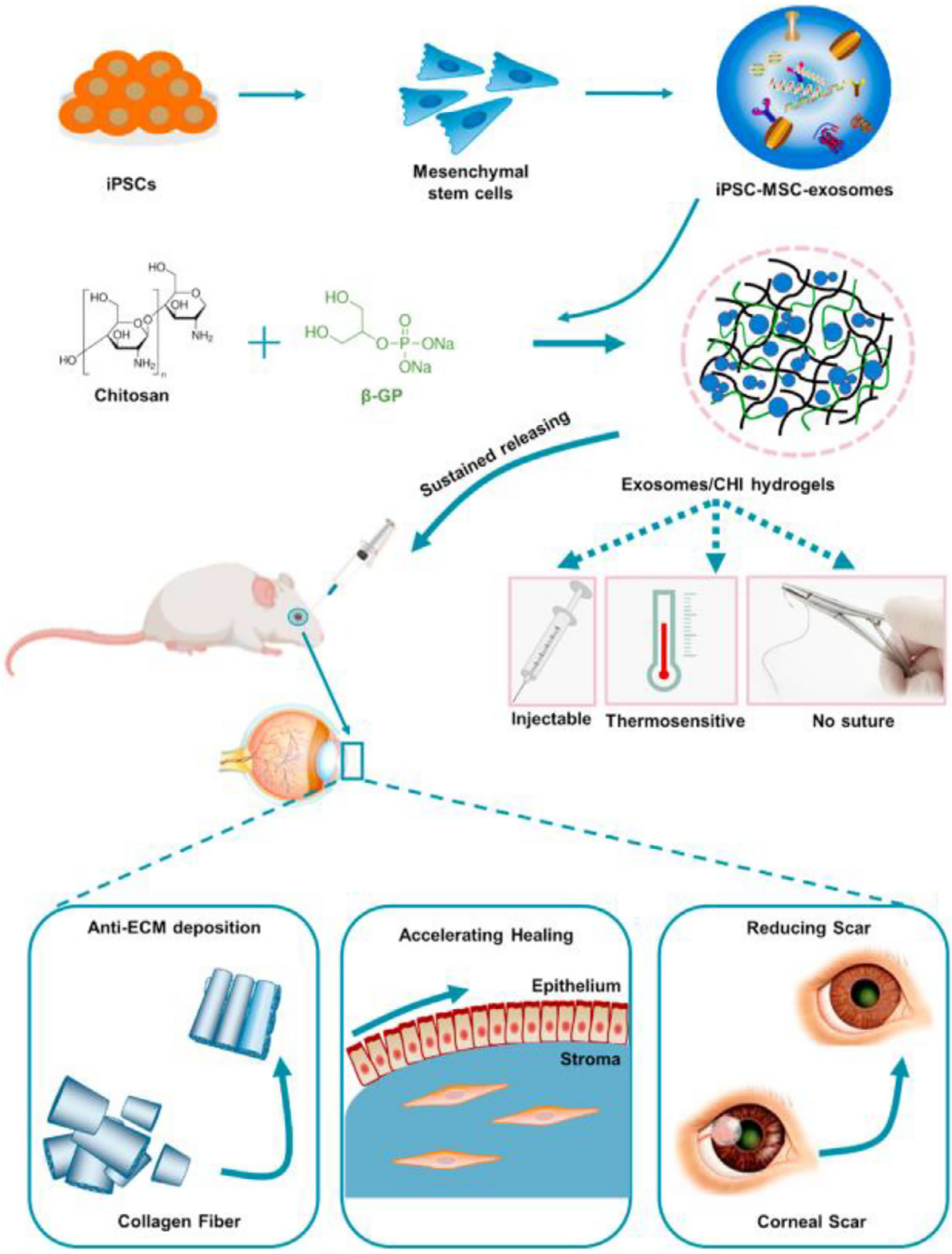

Fig. 11 – Thermosensitive hydrogels for ophthalmic diseases. Overview of the development of an iPSC-MSC-exosomes hydrogel for corneal regeneration [135]. Copyright 2022 Elsevier.

be altered by the incorporation of various nanoparticles or bioactive moieties [97,109]. This would lead to uncertain safety *in vivo* of lab-synthesized hydrogel preparations and hinder approvement for phase I clinical trials from Research Ethics Boards.

What is more important in our opinion, some drawbacks also limit the wide application of thermosensitive copolymers to a certain extent. For example, commercially available thermosensitive hydrogels (Pluronics or Poloxamers) have been used for the sustained delivery of multiple cells and drugs for many years. Unfortunately, there are some disadvantages that limit their utility in clinical to a certain extent, such as non-biodegradability and potential toxicity. To circumvent the disadvantages of common Pluronic hydrogels, various polymers based on Pluronics were synthesized by binding with biodegradable ester, carbonate, disulfide, urea, or urethane bonds [140–142]. Besides, in order to improve the degradability, PNIPAM, as one of the most broadly investigated

thermosensitive polymers, is often necessary to perform a significant chemical modification. Considering the nerve toxicity of residual acrylamide-like monomers, it seems rather hard to be commercialized in the future [96,108].

In addition, the degradation metabolites of triblock copolymer PCL-PEG-PCL may induce inflammatory responses *in vivo* [19,143]. These will result in the uncertain safety of hydrogel preparations *in vivo* and hamper the approval for clinical trials. Therefore, it is another prevailing trend to increase the degradability and biocompatibility of thermosensitive hydrogels while preserving the sol-gel transition properties.

5. Future outlook and summary

Precision therapy is the most attractive means among traditional chemotherapies, and it can greatly reduce the toxicity of normal tissues by avoiding the presence of chemotherapeutics in the systemic circulation. Thermosensitive hydrogels may be the best delivery platform because of their injectability, *in situ* gelation, and swelling behaviors triggered by temperature stimulus. To avoid leaks and ensure dose accuracy at the desired site, temperature sensitivity may be the research priority of thermosensitive hydrogels in the future. Meanwhile, the stability of hydrogels at room temperature is equally important which can affect crystallization and syringeability. Generally, thermosensitive hydrogels can only respond to the change in temperature. Thermosensitive hydrogels with more sensing functions, *e.g.*, pH, light, electrical, magnetic, pressure, ionic strength, chemical and biological stimulations, may remain the most promising for complex biological applications.

In this review, we summarized the recent advances in typical thermosensitive assemblies and the biomedical applications of thermosensitive hydrogels. Alteration in hydrogen bonds induced by temperature, electrostatic interactions, and molecular conformations are the main driving forces for the phase transition of thermosensitive hydrogels. Precision therapies through thermosensitive hydrogels, including wound healing, anti-tumors, bone regeneration, buccal, nasal, and ocular diseases, have been extensively introduced in diverse medical fields. However, the potential applications are not limited to these categories. For example, some skin diseases, such as psoriasis with irregular surfaces, microneedles, and traditional hydrogel sheet patches are not suitable for these uneven or large areas of skin disease. All the above limitations provide a potential opportunity for the wide application of thermosensitive hydrogels. We expect that more smart thermosensitive hydrogels will be designed in the future and make greater contributions to precision therapy for better ease of clinical translation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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