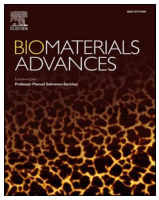
Biomaterials Advances 161 (2024) 213869

Contents lists available at ScienceDirect

Biomaterials Advances

journal homepage: www.journals.elsevier.com/materials-science-and-engineering-c



Review

# Enhancing regenerative medicine with self-healing hydrogels: A solution for tissue repair and advanced cyborganic healthcare devices

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A B S T R A C T

Considering the global burden related to tissue and organ injuries or failures, self-healing hydrogels may be an attractive therapeutic alternative for the future. Self-healing hydrogels are highly hydrated 3D structures with the ability to self-heal after breaking, this property is attributable to a variety of dynamic non-covalent and covalent bonds that are able to re-linking within the matrix. Self-healing ability specially benefits minimal invasive medical treatments with cell-delivery support. Moreover, those tissue-engineered self-healing hydrogels network have demonstrated effectiveness for myriad purposes; for instance, they could act as delivery-platforms for different cargos (drugs, growth factors, cells, among others) in tissues such as bone, cartilage, nerve or skin. Besides, self-healing hydrogels have currently found their way into new and novel applications; for example, with the development of the self-healing adhesive hydrogels, by merely aiding surgical closing processes and by providing biomaterial-tissue adhesion. Furthermore, conductive hydrogels permit the stimuli and monitoring of natural electrical signals, which facilitated a better fitting of hydrogels in native tissue or the diagnosis of various health diseases. Lastly, self-healing hydrogels could be part of cyborganics – a merge between biology and machinery – which can pave the way to a finer healthcare devices for diagnostics and precision therapies.

## 1. Introduction

Tissue engineering & regenerative medicine aim to address some challenges in medicine such as tissue and organ failure [1]. The current solution to those problems is mainly based on medication, surgical repair, artificial prostheses, mechanical devices or transplantation. Unfortunately, aforementioned options do not fulfill all the requirements to totally repair or recover lesions; as well as, they do not regenerate the tissue accordingly or they can present drawbacks such as infections and pain depending on the chosen treatment [2]. Although a number of obstacles still haunt this path, tissue engineering may help to progress in this unmet medical need. Tissue engineering has a multidisciplinary approach involving many fields (such as biology, chemistry, engineering, medicine, pharmaceutical and material science) in order to conceive novel therapies or products [1–4].

Among the vast array of opportunities that tissue engineering brings, the use of scaffolding systems with the aim to regenerate damaged tissues is gaining importance [1]. Those systems usually consist of three-dimensional (3D) structures fabricated to comply with various functions such as promoting cell-biomaterial interactions, allowing cells to survive (sufficient transport of gases, nutrients and regulatory factors), owing a good biodegradability and avoiding inflammation or toxicity [1]. In brief, these structures serve as an artificial extracellular matrix (ECM) to organize cells in a 3D manner, which can guide the growth and formation of new native tissue [5,6].

Hydrogels can achieve many of these goals due to properties including high water retention, resemblance to human's tissues' ECM, biocompatibility and biodegradability [4–10]. There are two types of gel sources to form materials: natural and synthetic. The chemistry, gelling conditions, and degradation of each type is very different. Synthetic polymers have a controllable and reproducible chemistry thus scientist can fine-tune hydrogel properties [5,8], but they may, from time to time, fail being biocompatible. Poly(ethylene glycol) (PEG), poly(L-lactic acid) (PLLA) or poly(vinyl alcohol) (PVA) are some examples of

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https://doi.org/10.1016/j.bioadv.2024.213869
Received 26 December 2023; Received in revised form 8 April 2024; Accepted 19 April 2024
Available online 22 April 2024
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synthetic materials [5,10]. On the other hand, natural polymers are known for being biocompatible, since they are often part of human tissues, but they lack the controllability of synthetic ones [5,8,10]. Chitosan, collagen, gelatin or hyaluronic acid are representative polymers of natural source [10]. Whatever type of hydrogel is chosen, it must meet some physical and biological properties [4,8,10], including: biocompatibility, degradability, suitable mechanical properties (which depends on the polymer chains, cross-linking molecules and bonds density), and capacity to interact with cells (which may enhance cell adhesion, migration and differentiation). To achieve the latter, hydrogels must have cell-specific ligands or have the ability of absorbing molecules with those ligands [10]. Conventional hydrogels sometimes cannot achieve those structural and functional properties, also they break easily within the body when they have to endure load-bearing and dynamic conditions [7]. Furthermore, permanent bonds within the hydrogel are a hindrance when it comes to regenerating human tissues [11].

The design and fabrication of self-healing hydrogels may help to overcome some of these limitations. Self-healing hydrogels have the ability of totally heal after a break or lesion, as some of human own tissues do. In comparison to traditional hydrogels, hydrogels with self-healing ability can automatically restore their structure due to dynamic/reversible linkages within the network [7,12–14]. Non-covalent interactions (hydrogen bonding, ionic bonding and hydrophobic interactions) and some covalent bonds (chelation and dynamic covalent bonding) are some of the most frequently used mechanisms [7]. In addition, there is another method to achieve strength and self-healing hydrogels: double network structures, created by coupling a strong network with a weak one consisting on reversible crosslinks [7,15,16]. Reversible bonding can increase hydrogels lifetime and endurance, endowing it with the ability to be injected [12]. The addition of nanomaterials can further improve the functionality of self-healing hydrogels, providing them with properties such as adhesiveness or electrical conductivity, which enables the development of multifunctional systems to heal tissues and organs [7,12]. Nanoreinforced hydrogels with electrical conductivity properties can also provide new alternative systems with different applications for self-healable electronics, cyborganics and soft robotics [7].

Herein, we summarize current applications of self-healing hydrogels platforms to mend tissue defects. Although there are many types of self-healing hydrogels, the target of this review paper is on self-healable hydrogels as delivery platforms focused on mending tissues such as bone, cartilage, nerve and skin. Moreover, it is also the aim of this review to highlight groundbreaking applications of these novel structures of self-healing hydrogels in mending tissues, targeting surgery and monitoring.

## 2. Self-healing mechanisms

Materials with self-healing properties have the ability of restoring their structure after being subjected to micro- or macro-fractures. The self-healing occurs when, within the matrix, bond connections re-link upon disruption. These bonds are typically formed by local mass transfer and re-linking of disrupted chemical bonds intervened by intrinsic noncovalent and/or covalent bonds [7]. Albeit, some self-healable hydrogels also need other extrinsic triggers to stimulate the healing process, such as UV-light, temperature and pH stimuli. The self-repairing mechanisms of the self-healing hydrogels were already extensive discussed by several authors [17–21]; thus, in this section, Table 1 summarizes the intrinsic self-repairing mechanisms behind self-healable materials.

## 3. Current applications of self-healing hydrogels to mend tissue defects: delivery platforms

Self-healing hydrogels have been investigated as possible candidates to mend various tissue defects. Although there are many types of self-healing hydrogels, the target of this section will be self-healable hydrogels focused on tissues such as bone, cartilage, nerve and skin, which play a role as delivery platforms of chemical/physical/biological agents including proteins, drugs, nanomaterials or living cells.

### 3.1. Self-healing delivery platforms for bone tissue engineering

The increasing age of the population is leading to a significant rise in bone-related injuries [38]. The current benchmark for addressing bone lesions is still autologous bone grafting, despite its potential drawbacks (variable clinical outcomes, postsurgical morbidity, reduced bioactivity or the risk of infections, among others) [4,39,40]. Bone tissue engineering can be crucial to get over those obstacles by creating new bone-related functional systems. For example, the use of self-healable hydrogels to support the load-bearing and dynamic native environment of bone could promote the healing process of the tissue [7,41].

Self-healing hydrogels for bone tissue engineering [18] are based on both non-covalent links [26,27,42,43] and dynamic-covalent bonds [44,45], as well as double network method [46]. To create these hydrogel systems, researches have explored a wide range of natural polymers such as hyaluronic acid (HA) [47,48], gelatin [39,44], silk fibroin [42,45] or alginate [44,49]. Moreover, there are also studies where hydrogels are fabricated using synthetic polymers such as poly (ethylene glycol) (PEG) [27,45,50].

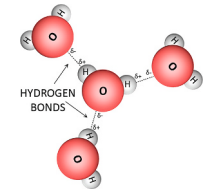
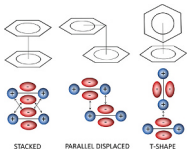
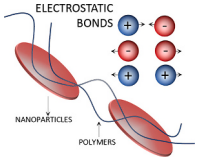
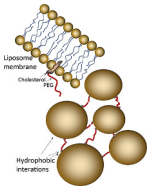
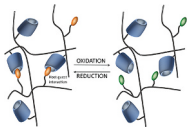
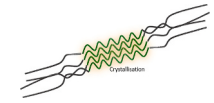
Self-healing hydrogels have shown great potential as drug carriers. Ren et al., created an injectable oxidized alginate hydrogels embedded with hydroxyapatite and calcium carbonate microspheres to act as tetracycline hydrochloride vehicle [44]. The system had self-healing properties due to dynamic Schiff-base reaction and it was able to delay the burst release of the antibiotic. Subsequently researches concluded that the created gel could be useful for bone regeneration [44]. In another study, Liu and co-workers fabricated a liposome-based hydrogel system as an anti-tubercular drug delivery platform [27]. Isoniazid (anti-tubercular drug) treatment is complicated due to side-effects, the quick elimination and the non-specific distribution within the body [51]. To overcome those inconveniences, researches created a PLGA-PEG-PLGA copolymer and incorporated isoniazid-loaded liposomes. Compact hydrophobic structures allowed a self-healing capacity and thermoresponsive ability, which made the system appropriate for tuberculosis therapy [27]. Conversely, Yang et al., developed an injectable chitin hydrogel as stem cell carrier [35]. The self-healing mechanism was based in dynamic acylhydrazone crosslinking. The construct exhibited injectability, self-adaptation and great *in vitro/in vivo* enzymatic degradability, which made the system a propitious tool to locally release biological/chemical therapeutic cargos or cells [35].

Other studies have also driven their efforts to create alternative delivery platforms. For instance, Wang and co-workers designed a self-healing hydrogel containing human umbilical cord mesenchymal stem cells derived exosomes in order to achieve a cell free therapy for bone regeneration [45]. The hydrogel was fabricated based on coralline hydroxyapatite (CHA)/silk fibroin (SF)/glycol chitosan (GCS)/ disfunctionalized polyethylene glycol (DF-PEG) in which the self-healing mechanism consisted of dynamic covalent imine bonds. This system showed effectiveness promoting bone reconstruction in *in vivo* studies, owing to its capacity to stimulate bone morphogenic protein 2 (BMP2) deposition, bone collagen deposition/maturation and angiogenesis [45]. Further, Li and colleagues set up a strength, injectable and self-healing hydrogel with the ability to act as a delivery platform; this was built mixing alginate dialdehyde (ADA) with borax and gelatin, thus creating a double cross-linked structure (dynamic Schiff base and the borax ion) [49]. The system was loaded with demineralized bone matrix (DBM) powder and hypoxia-pretreated bone marrow stromal cells, both *in vitro* and *in vivo* results showed that this strategy allows a good bone regeneration effect in comparison to the controls [49].

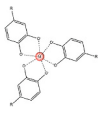
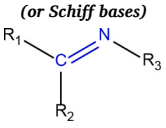
Recent studies have shed new light on the potential of nanomaterial-

**Table 1**
Intrinsic self-repairing mechanisms of self-healable hydrogels.

Physical noncovalent crosslink interactions
*(usually based on weak links)*

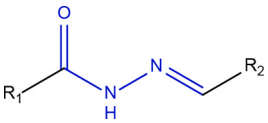
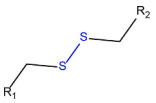
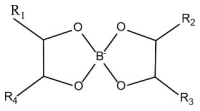
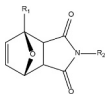
| Types | Mechanisms | Considerations | Examples |
|---|---|---|---|
| ***Hydrogen bonds***   | Dipole-dipole attraction between molecules (electrostatic link); in other words, it is an intermolecular H-bonding involving positive H atom and highly electronegative atoms such as N, O or F. Examples of bonds between: carboxyl and amide groups (NH···O=C); two hydroxyls (OH···OH); H and F (H···F). | -Weak interactions, but easy and fast association-dissociation-association of H-bonds;<br>-Can usually act as a secondary crosslink (contributing to elastic mechanical properties);<br>-Need to be combined with other stronger bonds (forming double-network hydrogels). | Tannic acid/ O-carboxy-methyl chitosan-based hydrogel [22]. |
| ***π-π stacking interactions***   | Interactions involving π bonds of the aromatic rings, which can be in T-shape, parallel-displaced or in sandwich configurations. Possible materials: graphene, CNT and polymers containing aromatics. | -Can be weaker than H-bonds;<br>-Can also occur interaction with peptide-based and among other biological molecules. | Phenol- chitosan/ dibenzaldehyde telechelic PEG [23]. |
| ***Ionic bonds***   | Reversible electrostatic bonds between oppositely charged functional groups or moieties of polymers, as well as both these with charged nano-materials (nanocomposite hydrogels). Note: ionic bonds can be between the same polymer (when presenting both positive and negative polarities). | -Easy procedure;<br>-Inclusion of nanomaterials can increase hydrogel's toughness and stability and brittleness (but this can be mitigated by inclusion of other material with chemical covalent crosslink, thus forming double-network hydrogels). | Cellulose nanocrystal based triple-network ion gel.<br>Nanoreinforced hydrogels with Laponite® [24–26]. |
| ***Hydrophobic interactions***   | Micelle-like schemes: reversible interactions of hydrophobic moieties<br>(cyclic association-dissociation-association of the micelles).<br>Note: host-guest interactions comprise hydrophobic interactions too, but with distinct hydrophobic arranging (host-guest-like schemes, see below). | -Easier to control and slightly stronger than H-bonds;<br>-Yielding hydrogels' properties: playing with hydrophobic moieties ratio and their shape;<br>-Great candidate for hydrophobic drug delivery. | Liposome-in-hydrogel system was created as isoniazid carrier for localized treatment [27]. |
| ***Host–guest interactions***   | Conjugation of cyclodextrin structures with hydrophobic guest molecules where these being hosted within hydrophobic inner cavity. Further, host-guest interactions can also comprise other links (*e.g.* π-π stacking & H-bonds). | -Complex interactions;<br>-Concern: low water-uptake (get better if balance of hydrophilic/ hydrophobic ratio);<br>-Possibility of macrocyclic hosting one or more guest molecules.<br>-Great candidate for redox- responsive hydrogels development. | Silk fibroin based acryloyl-β-cyclodextrin (Ac-CD) and 2-hydroxyethyl acrylate hydrogel [28]. |
| **Crystallisation**   | Specific and organised self-assembly, with crosslink between polymer chains. Note: this interaction also comprises as subdivision of other links because follow distinct links; *e.g.* H-H-bonds (freeze-thawing), ionic-ionic, hydrophilic/ hydrophobic interactions. | -Yielding hydrogels properties: crosslink-type, arranging, polymer-type. | Polyvinylalcohol(PVA)/Agar/ Graphene nanocomposite hydrogel [29]. |

**Chemical covalent crosslink interactions**
***(based on dynamic covalent bonds and metal coordination bonds)***

| **Types** | **Mechanisms** | **Considerations** | **Examples** |
|---|---|---|---|
| ***Chelation***  | Involve bonds-coordinated where one positively charged transition-metal ion is surrounded by ligands (organic molecules) yielding complex lattices. | -Can provide strong interactions, as well as elasticity and adhesiveness. | $Fe^{+3}$ (linker) & hyaluronic acid (network) [30,31]. |
| ***Imine bonds (or Schiff bases)***   | Involve reversible covalent bond formation by aldehyde group and primary amine. | -Dynamic covalent reactions that can occur at both neutral and acidic pH medium. | PF127/ PEI & aldehyde pullulan.<br>Chitosan/ benzaldehyde-PF127 [32,33]. |
| ***Acylhydrazone bonds*** | | | |

(*continued on next page*)

**Table 1** (*continued*)

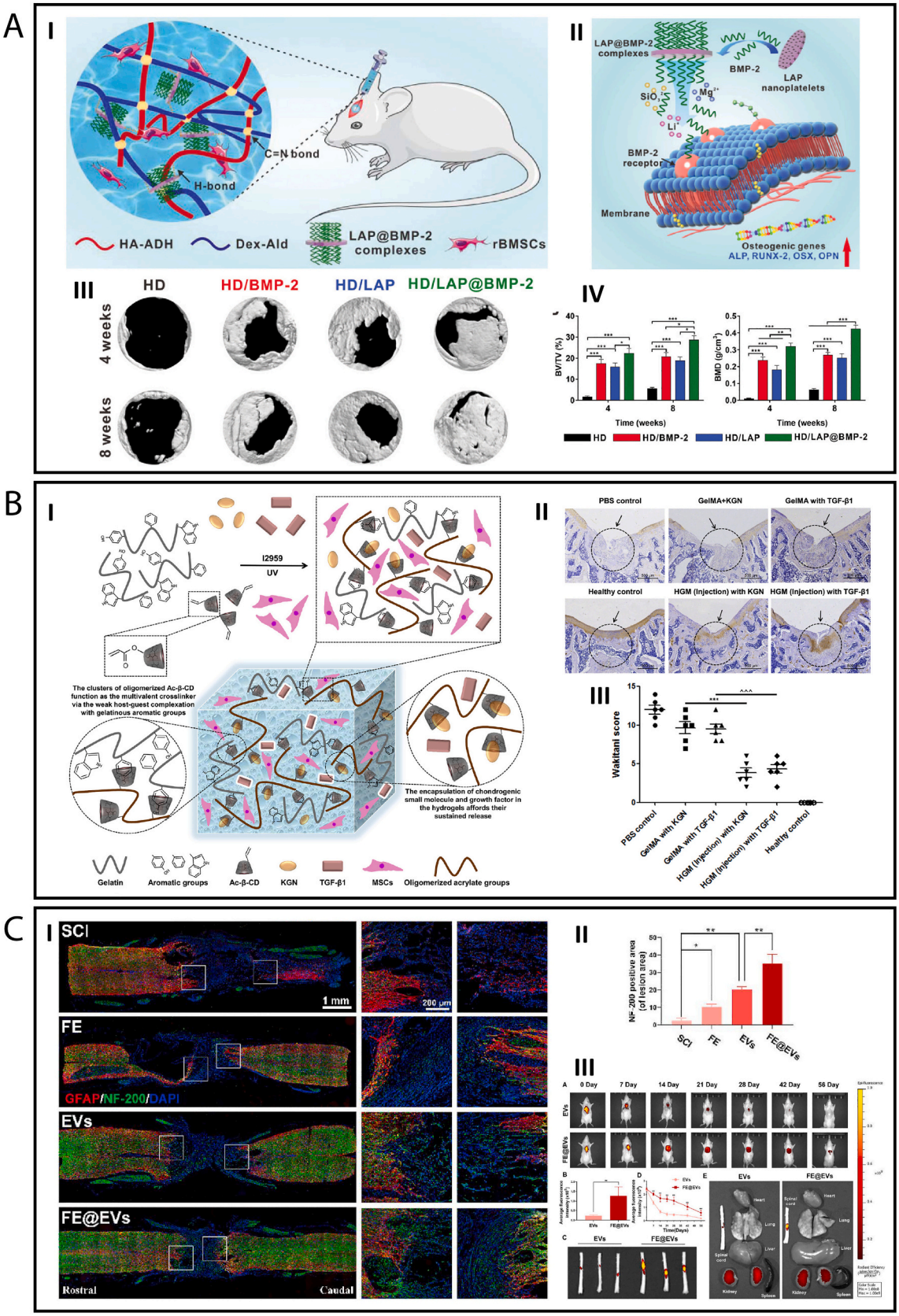
| **Chemical covalent crosslink interactions** *(based on dynamic covalent bonds and metal coordination bonds)* | | | |
|---|---|---|---|
| **Types** | **Mechanisms** | **Considerations** | **Examples** |
|  | Involve reversible covalent bond formation by typically condensation reaction of hydrazine (or hydrazide) with aldehyde (or ketone) groups. Acylhydrazide groups can be leveraged and formed simultaneously. | -Can spontaneously form under physiological conditions;<br>-Great candidate for temperature and pH-responsive hydrogels development. | ADH- carboxyethyl chitin. Chondroitin sulfate based F127@ChS/furan/ADH [34,35]. |
| ***Disulfide bonds*** | | | |
|  | Thiol-disulfide dynamic exchange reactions (reversible covalent bond formation), from of oxidation of two sulfhydryl groups. | -Might not have good stability in physiological tissues (due to the glutathione presence, reducing agent). | 4-arm-PEGSH dynamic hydrogel [36]. |
| ***Boronate esters*** | | | |
|  | Form reversible covalent bonds by the combination of boronic acid and diols. | -Great candidate for pH-responsive hydrogels development, since is highly pH-sensitive. | O-carboxy-methyl chitosan/ TA/ 1,4-benzenedi-boronic acid [22]. |
| ***Diels–Alder reactions*** | | | |
|  | Conjugated reaction between diene (HOMO) and a dienophile (LUMO) compounds; electrocyclic reaction that comprise π electrons. | -Click reactions that are promising for injectable delivering;<br>- Thermally reversible bonds. | Cellulose nanocrystal-PEG hydrogel [37]. |

based self-healing hydrogels. Within the mineral-based nanomaterials, nanoclays (silicate-based nanoparticles) may be an interesting approach for bone tissue regeneration [7,52,53]. Furthermore, nanoclays' ultra-thin morphology and high surface area to volume ratios make them profitable for improving the mechanical characteristics of biomedical systems [54,55]. Apart from silicate, nanoclays contain minerals (magnesium, calcium, lithium and zinc) that are part of bone native tissue [52,55]. Silicate controls collagen synthesis, mineralization of bone matrix and some osteogenic processes. For example, magnesium ions can stimulate osteogenesis activating HIF-1α and PGC-1α pathways and ligand binding of integrin subunits, while lithium ions can inhibit glycogen synthase kinase-3 (GSK3), which finalizes activating the osteogenic transcription factor runx2 [52]. Thus, promoting the physical release of these elements is imperative for a better bone regeneration therapy [52,55].

Self-healing mechanism behind nanoclay-reinforced hydrogels is often driven by ionic interactions. The latter occur between the positive and negative charged parts of the nanoclay with the polymer backbone; but, it can also be created due to the high-surface area of the nanoclays [7]. As it is the case of Laponite® RD (trademark of the company BYK Additives Ltd.), one of the most frequently used nanoclay as part of self-healing hydrogels. Indeed, Lee et al., produced nanoclay-organic hydrogel bone sealant (NoBS) for bone healing purposes, and this hydrogel was composed of phytochemical-modified organic chitosan and silica-rich inorganic Laponite® RD [26]. The self-healing ability was based on dynamic noncovalent and covalent interactions between nanoclay-polymer and polymer-polymer networks. Laponite® RD enabled a delayed and controlled smoothened agonist (SAG, as a model drug) release because of ion exchange among cations ($Ca^{2+}$, $Na^{+}$, $K^{+}$ and $Mg^{2+}$) and the drug. *In vivo* results showed that NoBS hydrogel loaded with SAG had osteoinductive capability for enhanced bone regeneration [26]. In a similar vein, Zandi and colleagues created a bioprintable hydrogel based on glycosaminoglycan nanoparticles and Laponite® RD that acted as a cell carrier [56]. The system displayed a quick recovery response, as well as shear-thinning and viscoelastic properties and it resulted to be biocompatible and bioactive, which derived in favorable *in vitro* and *in vivo* results [56]. Otherwise, Zhang and co-workers designed a chitosan and Laponite® RD system to deliver demineralized bone matrix (DBM) [43]. DBM consist on a combination of growth factors and protein matrix components (collagen type I, BMP-2 or osteopontin) and it is suitable for treating bone defects. Dynamic non-covalent bonds such as hydrogen bonds and electrostatic interactions allow the self-healing capacity of DBM-laden system. The construct displayed osteogenic abilities by activating Wnt/β-catenin pathway. Furthermore, *in vitro* tests such as Alizarin Red staining or ALP activity as well as the osteogenic gene expression analysis confirmed mouse bone marrow stromal cell (BMSC) line (D1) differentiation within the system, which demonstrated that DBM was effectively delivered. Consequently, it was concluded that the designed hydrogel was a resourceful system to act as drug, cell or therapeutic agent carrier [43]. In another study, Zhang et al. created hyaluronic acid-dextran- Laponite® RD -BMP2 hydrogels for non-invasive bone regeneration [48]. The capacity for self-regeneration was based on a Schiff-base reaction and the electrostatic interactions that Laponite® RD allows; in this way, the structure maintained its long-term integrity and decreased the risk of an invasive treatment. Apart from that, the clay allowed a sustained release of the growth factor. Researches embedded hyaluronic acid-dextran- Laponite® RD -BMP2 gels with rat bone marrow mesenchymal stem cells (rBMSC) to reach a synergistic effect on bone healing. *In vitro* test showed that the constant release of BMP-2 by the system enhanced the spreading, proliferation and osteogenic differentiation of rBMSC, while *in vivo* studies confirmed that newly formed bone was notably higher in hyaluronic acid-dextran-laponite-BMP2 hydrogels than in control groups, Fig. 1A. Given the results obtained from both *in vitro* and *in vivo,* it can be deduced that this system is an interesting approach for bone tissue engineering [48].

### 3.2. Self-healing hydrogels as carriers for cartilage tissue engineering

Cartilage is a resilient and smooth elastic tissue that lacks irrigation, nerves and lymphatic system, with a low cell density consisting mainly on chondrocytes [59,60]. The aforementioned characteristics and the composition of the cartilage (5 % of cells and 95 % of a dense ECM) make the tissue's ability to self-regenerate very limited [59,61]. There are several diseases affecting cartilage, osteoarthritis (OA) being the most common one, closely followed by rheumatoid arthritis (RA) [62]. The first is characterized by cartilage degeneration mainly in joints, which may lead to pain and loss of joint function, whereas RA consists on an




*(caption on next page)*

**Fig. 1.** (A) Hyaluronic acid-dextran-laponite-BMP2 hydrogels for bone tissue engineering: (I) schematic illustration of the studies carried out; (II) Picture showing the mechanism of the system for osteogenic differentiation; (III) *in vivo* representative images of calvarial bone defects at 4 and 8 weeks post-implantation, and (IV) morphometric analysis of bone volume/total volume (BV/TV). *$p < 0.05$, **$p < 0.01$ and ***$p < 0.001$ [Reproduced (adapted) from Ref. [48] with permission from the Royal Society of Chemistry, https://doi.org/10.1039/C9BM01455A] [48].
(B) Gelatin host-guest macromer hydrogel for cartilage tissue engineering: (I) Schematic illustration of cross-link method, cells encapsulation, chondrogenic molecules and growth factors in the created system; (II) Immunohistochemical staining against type II collagen of the rat knee osteochondral defects in control and different experimental groups, and (III) Cartilage regeneration estimated with Wakitani scoring system at week 6 after surgery [Reproduced (adapted)) from Ref. [57] with permission from Copyright Elsevier] [57]. (C) F127-polycitrate-polyethyleneimine hydrogel (FE, with hydrogen-bonding self healing mechanism) loaded with extracellular vesicle (FE@EVs, by electrostatic interactions) for nerve tissue engineering: (I) Immunohistochemical staining in injured spinal cord injury after 56 days post-injury; (II) Confirmation of long sustained release *in vivo* of the extracellular vesicles encapsulated in the injectable hydrogel, and (III) Quantification of NF-200 positive area at 56 days post-injury [Reproduced (adapted) from Ref. [58] 50 with permission from Bioactive Materials (KeWai) Science Direct] [58].

inflammation and deterioration of joints caused by an autoimmune disease [62]. Current therapies are palliative and do not avoid further degeneration of the tissue [61,62], thus fueling the need of new tissue-engineered approaches. Consequently, considering the aforementioned issues that cartilage tissue engineering and therapy usually face, self-healing hydrogels can be used as injectable cell-delivery platform working as minimal invasive clinical approaches to overcome those drawbacks. For example, with the breaking and re-linking of the chemical bonds the hydrogels can self-adapt during the injection due to shear-thinning properties, consequently it is less detrimental to cells, preserving the cells viability and possibility of multiple injections in complicate cases.

For the treatment of OA, Mohamed and colleagues produced a mesoporous silica nanoparticles/hydrogel loaded on cotton fabrics for colchicine delivery [63]; as in the case of isoniazid, there are some difficulties in the administration of colchicine such as side-effects and patient's incompliance. The hydrogel based on carboxyethyl chitosan/oxidized pullulan showed self-healing ability as it was formed *via* dynamic imine bonds (through Schiff base reaction, between amino group from carboxyethyl chitosan and aldehyde groups from pullulan). Moreover, the system displayed *in vitro* & *in vivo* results accomplishing an efficient and safe OA therapy [63]. Following the same line, Zhao et al., combined three-dimensionally (3D) printed scaffold with infliximab loaded hydrogel [64]. The self-healing ability of the structure was formed through dynamic reactions of modified polysaccharides (hyaluronic acid-hydrazide reacted with hyaluronic acid-aldehyde *via* acylhydrazone-based bonds) and the drug (where amino groups of infliximab reacted with hyaluronic acid-aldehyde, *via* imine bonds). This approach displayed favorable biocompatibility *in vitro* and reduction of inflammation *in vivo,* so researches concluded it was a promising option for large-scale bone defects caused by RA [64].

For articular cartilage repair, Fig. 1B, Xu et al. designed a system capable of sustaining a co-delivery of chondrogenic molecules (kartogenin and TGF-β) in order to enhance the chondrogenesis of encapsulated human bone marrow mesenchymal stem cells [57]. The gelatin macromer hydrogel was formed *via* host-guest interaction between Acrylate-β-cyclodextrin (Ac-β-CD) and the aromatic residues of gelatin. Then, it was exposed to UV light for 10 min to get the oligomerization of the acrylate groups of Ac-β-CD. The host-guest crosslink was responsible of the injectability and self-healing capacity of the system, while the hydrophobic cavities of host-guest macromer allowed a constant release of hydrophobic molecules as kartogenin. *In vivo* results demonstrated that hydrogels maintained the integrity of the structure after 28 days and supported neocartilage formation in a rat cartilage defect model, showing that the system had potential for cartilage regeneration objectives with a minimally invasive procedure [57].

Kim and co-workers fabricated a bioprinted cell-laden and self-healing hydrogel for tissue engineering applications, including cartilage [65]. They used a Schiff base reaction between oxidized hyaluronate (OHA) and glycol chitosan (GC), as well as acylhydrazone bonds between OHA and adipic acid dihydrazide (ADH), forming self-healing systems showing 100 % of rheological recovery when ADH content reached at least 0.3 % in the composition. The construct promoted the chondrogenesis of encapsulated ATDC5 line cells and displayed good stability without a secondary cross-linking, so it showed potentiality for cartilage tissue engineering applications [65]. In a similar way, Zhang and colleagues, produced a cell delivery platform based on cellulose nanocrystals and collagen [66]. The Schiff base reaction between the aldehyde on the surface-modified cellulose nanocrystals (CNCs) – and amine groups on lysine or hydrolysine of collagen gives self-healing ability and injectability to the system, as well as an increase of >2.5-fold on the storage modulus. The nanocomposite hydrogel was able to fit in irregular cartilage defect and to protect cells within it. These properties made the cell delivery platform a great tool for cartilage regeneration [66].

Eventually, as in the case of bone, nanoclays may play an important role in the generation of new self-healing hydrogels for cartilage healing. Boyer et al. created a Laponite® RD -reinforced hydrogel for cartilage tissue engineering [67]. Researches encapsulated human nasal chondrocytes (hNC) within the silated hydroxypropilmethyl celulose (Si-HPMC) and nanoclay hydrogel, thus creating a hybrid interpenetrating network system. The addition of the clay enhanced the mechanical properties of the gel, and was able to maintain, in a limited manner in comparison to hydrogels without the clay, the cells alive for 6 weeks *in vivo.* These results were encouraging for new cartilage therapies, but there is still much to investigate, specially about the potential toxicity of the clays [67].

### 3.3. Self-healing delivery platforms for nerve tissue engineering

Neurological injuries are a prevailing clinical problem worldwide, causing morbidity and considerable financial burden [68,69]. Peripheral nerve system has a limited self-healing ability, and central nerve system lacks the capacity of self-regenerate [68,69]. Autologous nerve graft is the gold-standard treatment, but it presents some drawbacks (such as the lack of good quality grafts and the accessibility to them); hence, neural tissue engineering has come up to cover this medical area [68].

Self-healing hydrogels have demonstrated utility in nerve tissue regeneration. For instance, Liu et al., had designed a semi-interpenetrating polymer network based on natural polymers for central nervous system (CNS) repair [70]. The system possesses self-healing ability due to the crosslinking of glycol chitosan and dysfunctional poly(ethylene glycol); besides, the addition of hyaluronan gave hydrogel the ability to promote CNS regeneration. Possibly this was due to the addition of hyaluronan, which could provide a permissive microenvironment to support axonal adaptions and axonal growth. Moreover, hydrogel's composition could also provide therapeutic effects, so inducing less inflammatory response [70]. The created self-healing hydrogel showed injectability, and promising results *in vitro* and *in vivo*, exhibiting potential for nerve tissue engineering; for example, using rat intracerebral hemorrhage (ICH) model, it was applied saline solution (as control) and self-healing hydrogel, after 14 days of injection while the control showed 40 % of behavioral function recovery the hydrogels showed >70 % of behavioral function recovery [70]. Interestingly, Xuan and co-workers fabricated a self-healing hyaluronic acid and silk fibroin coating [71]. The coating was formed with layer-by-layer self-assembly, and host-guest interactions between the polymers

allowed the self-healing ability. The structures not only displayed excellent biocompatibility and antibacterial capacity, but also showed enhancement of cell proliferation and myelination of Schwann cells (with PMP22 protein level almost double for the self-healing hydrogels in comparison to the control), which made it a suitable choice for nerve regeneration [71].

In addition, with the aim of preventing epidural adhesion due to laminectomy, Wang and colleagues created a multifunctional supramolecular hydrogel [72]. There is a need to develop antifibrotic and anti-adhesive materials to turn aside neural adhesion. This hydrogel was based on Poloxamer 407 (a triblock copolymer), with anti-inflammatory and anti-oxidative stress nanoparticles (TPCD NPs) and tannic acid as adhesive agent. The system presented sustained nanoparticle release and degradation until 7 days, as well as advantageous properties like adhesiveness, self-healing ability, anti-inflammatory and anti-fibrotic abilities (with >2.5-fold lower than the control) [72].

In the area of self-healing delivery platforms, a recent study showed the utility of F127-polycitrate-polyethyleneimine hydrogel to deliver mesenchymal stem cells derived extracellular vesicles (Fig. 1C). Hydrogels were tested to mend spinal cord injuries due to its biocompatibility, injectability, adhesive behavior and high extracellular vesicle loading/binding [58]. The benefits of delivering extracellular vesicles (paracrine secretions of cells) in tissue engineering application as therapeutic delivery systems is because apart of having a better interaction with the cell membrane than other synthetic nanoparticles, they are richly loaded of therapeutic biological cargos (such as mRNAs, miRNAs, and proteins) that can support tissue regeneration [58]. During the *in vivo* studies focused on remyelination investigation, upon application of self-healing hydrogel alone, myelin basic protein (MBP) showed relative level around 0.5, while the negative control (spinal cord injury) was around 0.15 and positive control (sham) around 0.9. Consequently, the results presented the positive influence of using self-healing hydrogels to promote nerve tissue engineering. Moreover, using the self-healing hydrogels combined with exosomes as a delivery platform, the MBP relative level was around 0.9, similar to the positive control, and higher than the exosomes alone 0.75 [58].

### 3.4. Self-healing delivery platforms for skin tissue engineering

Skin is the largest organ in human body; moreover, skin tissue has one of the highest regenerative potential, even though it is the one of latest of being explored. Nevertheless, although skin is not considered a vital organ, skin tissue engineering is not less important. Skin tissue engineering can be used to address many medical issues, such as treatments for post burn events and diabetic wound dressings. Notably, bearing in mind that skin tissue regeneration is a complex stepwise process (which involves, hemostasis, key inflammatory-paths, proliferation and remodeling), it is also required special attention to avoid bacterial infection since detrimental effects go beyond ordinary inflammation phase in tissue regeneration process. For example, a bacterial inflammation can be extended to the whole regeneration process by unbalancing of pro- and anti-inflammatory cytokines, which enrolls significantly M1 polarization and postponing the arrival of M2 to support the immunomodulation phase for the regeneration process. Consequently, when creating self-healable hydrogels to mend skin impairment, having an antibacterial ability is one of the most important requirement. As a consequence, much effort has been devoted to design and test hydrogels with antibacterial properties [73–77]. In the majority of attempts, the hydrogels itself already have this antibacterial feature in their composition, thus creating a self-therapeutic delivery platform. For example, enzyme-assisted dual-network self-healing hydrogels obtained thanks to dynamic covalent interactions (*i.e.* Schiff base reactions and hydrogen-hydrogen bonds) showed antimicrobial activity against both Gram-negative (such as *Escherichia coli*) and Gram-positive bacteria (such as *Staphylococcus aureus*) due to the presence of e-poly-L-lysine (EPL) in its composition [78]. It is well-known that silver nanoparticles have antibacterial properties, Yue Zhao et al. have used this tool to develop, as diabetic foot wound dressing and as epidermal sensor, a conductive tissue-adhesive hydrogel with polydopamine decorated silver nanoparticles for antibacterial activity against Gram-negative and Gram-positive bacteria [79].

Above and beyond, self-healable hydrogel was also developed using ethylenediaminetetraacetic acid (EDTA) − $Fe^{3+}$ complexes cross-linked with hyaluronic acid (HA), where this dynamic coordination interaction between $Fe^{3+}$ and COOH presented a system which could cause inhibition of microbial infections (kill *E. coli* and *S. aureus*) [30]. This was possible due to the local degradation and release of $Fe^{3+}$, which induced Fenton oxidation in bacteria. Likewise, the hydrogel system disposed of a sustained control release of platelet-derived growth factor two B subunits (PDGF-BB), thus promoting angiogenesis and tissue regeneration [30]. Zhao et al. designed a tissue-adhesive hydrogel with self-therapeutic delivery platform, based on catechol-$Fe^{3+}$ coordination, cross-linked poly(glycerol sebacate)-*co*-poly(ethylene glycol)-*g*-catechol and quadruple hydrogen bonding crosslinked ureido-pyrimidinone modified gelatin. There, the $Fe^{3+}$ was used to physically crosslink catechol groups, in order to retain catechol-unoxidized groups to develop hydrogels with antioxidant activity to promote skin wound repair. Moreover, with this catechol–$Fe^{3+}$ coordination crosslinking hydrogel, it was possible to develop a photothermal-responsive delivery platform with antibacterial competence aimed to act against methicillin-resistant *Staphylococcus aureus* (MRSA) [31]. Furthermore, some properties of the hydrogels (including anti-oxidative activity, hemostatic property and tissue adhesion) also stimulated tissue repair process. Overall, the hydrogels presented more fibroblast migration, angiogenesis, weaker inflammatory infiltration and thicker granulation tissue, as well as dermal tissue with new skin appendages (with largest number of hair follicles) when compared to control groups.

Smart multifunctional self-healing hydrogels that can assist wound closure and wound healing have also been created [73]. Such system display a number of relevant functions including anti-infection, anti-oxidation ability, as well as temperature-dependent drug release ability by Fickian diffusion. This was observed using the antibiotic doxycycline (Doxy, as model drug) to evaluate drug release performance (*in vitro*) from all of the hydrogels at both 25 and 37 °C. Notably, Wang et al. developed a self-healing hydrogel loaded with exosomes for treatment of diabetic severe wound infection and for improve healing, as well as to support angiogenesis. Exosomes are natural biological vesicles (from nano- to micrometers) secreted by cells – where their shell structure is composed of cellular-sourced membrane which contains receptor-ligand signals and transmembrane proteins, as well as their core fully loaded with precious biological cargos (such as, DNAs, RNAs, mRNAs, miRNAs, proteins, among others) – which means that the exosomes are theoretically supported to facilitate transfection-like of animal cells [80]. In summary, exosomes are considered a great biomaterial that takes part in all phases of tissue regenerations: (i) inflammatory, (ii) proliferation and (iii) remodeling processes. Likewise, in order to treat diabetic wounds and allow skin reconstruction, besides the antibacterial activity to eradicate MRSA, Wang et al. also developed an injectable and tissue-adhesive polysaccharide-based self-healable hydrogel. This hydrogel proved its capability as pH-responsive exosome sustained release, which was confirmed by *in vivo* studies, showing angiogenesis and diabetic wound healing [32].

In summary, besides skin tissue being the most external layer of the human body where antimicrobial properties are vital in the biomaterial, skin tissue is always intrinsically subjected to motion effect. Consequently, self-healing hydrogel application in skin tissue regeneration is suggested visioning less scar tissue formation due to its dynamic self-adaptability, which can promote a more realistic self-adaptable embodiment for the cells. On top of this, in case of deep skin injury, injectability of biomaterials is required; subsequently, visioning an ideal clinical scenario for cell-delivery therapy, self-healing hydrogels are less detrimental for the cells, preserving cell viability.

## 4. Emerging application of self-healing hydrogels to mend tissue defects: surgeries and monitoring

In tissue engineering & regenerative medicine, self-healing hydrogels have been investigated to mend tissue defects by supporting daily surgical procedure and clinical monitoring. In this section, the discussion will be focused on tissue-adhesive hydrogels, electrical conductive hydrogels and their application for tissue-cyborganics.

### 4.1. Adhesiveness

In parallel with the advancement of the self-healable hydrogels, self-healable tissue-adhesive biomaterials also emerged intending to mend tissue defects by supporting clinical procedures (such as in surgical closure and fixing biomaterial-tissue integration). Additionally, among the ongoing advances of medical tissue-adhesives, they are also being developed with versatile functionality to accomplish tissue repair, acting as hemostatic mediators and wound closure stimulators, promoting antibacterial effects and native tissue-like regeneration [72,73]. Outstandingly, the self-healable tissue-adhesive hydrogels have also been designed to achieve desirable injectability – targeting minimally invasive surgery – to easily fill and repair tissue imperfections, avoiding large surgical distress by solely managing them through needles and catheters. Conventional wound closure by suturing can cause considerable tissue distortion during and after surgical procedure, which can be painful, enhance fibrosis and difficult local healing. Nevertheless, substituting suture cables by tissue-adhesives diminishes these concerns and could take advantage of ease removal for further re-incision if needed, which could implicate less-time and less-cost for would closure, as well as benefiting for the improved patient recovery.

Several reviews have addressed and described adhesive biomaterials [81–86]. Most recently, Zhang et al. reviewed tissue-adhesive hydrogels for wound dressing and discussed about distinct-types of adhesion mechanisms [81]. Fig. 2 presents the major adhesion mechanisms in tissues and their classifications; which comprises essentially two main segments: (i) adsorption and (ii) mechanical interlocking, being many the subdivision of these mechanism segments. For example, Yan et al. focused on bioadhesive hydrogels development based on mussel inspired-adsorption mechanism, on which PLGA/ALG–CHO–Catechol self-healable hydrogel was developed for tissue-adhesive application from dopamine-grafted oxidized alginate and hydrazide-modified poly (L-glutamic acid) (PLGA–ADH). The system revealed good cytocompatibility, as well as anti-bleeding effect *in vivo* in a rat liver model [87].

Similarly, based on mussel inspired-adsorption mechanism, Chen et al. developed another tissue-adhesive hydrogel using dopamine-grafted oxidized alginate; but instead, they combined this with polyacrylamide (PAAm) for wound dressing. This hydrogel presented capability to adhere to various organic and inorganic substrates, such as skin, polymer, glass and metal, with adhesion range from 3.4 to 8.7 kPa. Furthermore, their hydrogel revealed potential for tissue regeneration *in vivo*, where the wound non-treated with hydrogel presented cell interstitial oedema and inordinate fibroblast, while the wound treated with hydrogel presented mature and compact collagen fibres and signs of faster healing [88].

Tissue-adhesive hydrogels have also been investigated for distinct tissue applications. Phadke et al. investigated hydrogels based on acryloyl-6-aminocaproic acid (A6ACA) as adhesive-systems for gastric tissue. A6ACA-based hydrogels disposed of pH-mediated healing at low-pH environment, thus with stomach perforations the tissue-adhesives activate to self-heal by hydrogen-bonded carboxyl groups to prevent leakage of gastric acids [89]. Although Phadke et al. have not specifically explored the potential ability of the tissue-adhesive A6ACA-based hydrogels for tissue regeneration, they investigated the biomaterial as potential drug carrier by loading tetracycline drug and exposing it at gastric-simulated low-pH environment, which resulted in a sustained release rate for 4 days [89]. In another study, Sun et al. explored a hydrogel that could be applied for emergency procedure of blood vessel closure. TA/PEG-SG tissue-adhesive hydrogels were formed by simply mixing tannic acid (TA) and 10 kDa eight-arm-poly(ethylene glycol) end-capped with succinimide glutarate active ester (PEG-SG) [90]. *In vitro* artery vascular closure was performed by applying a TA/PEG-SG

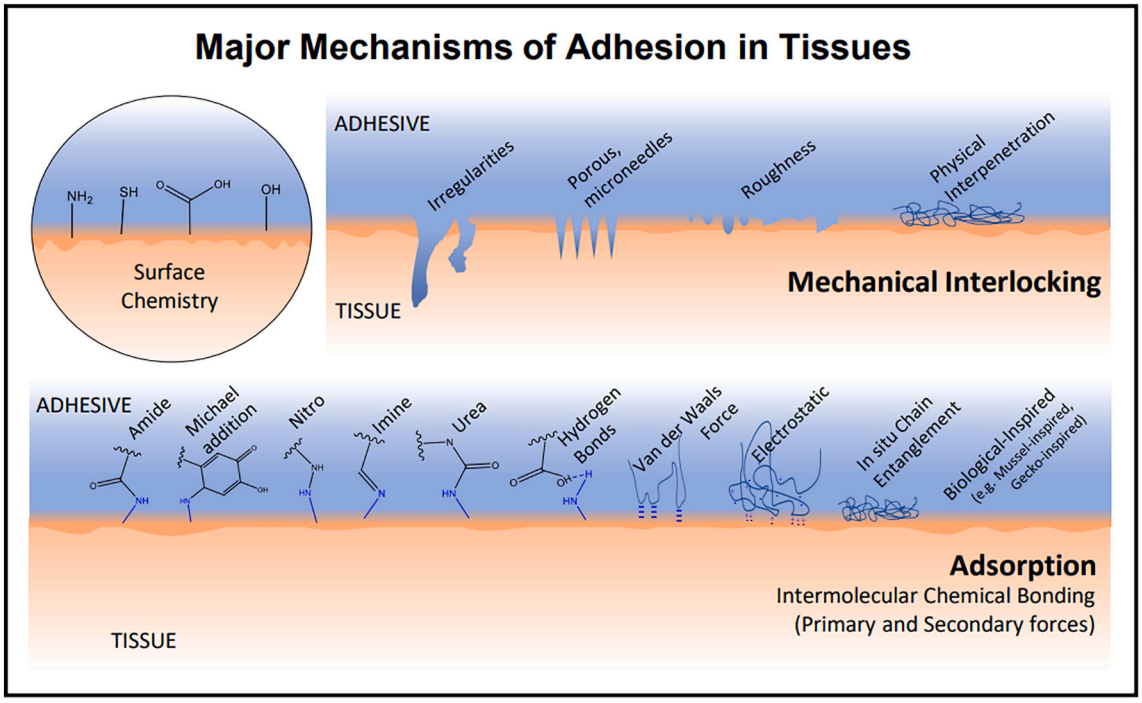



**Fig. 2.** Schematic illustration of major adhesion mechanisms of hydrogels for biological tissues, which involves essentially 2 mechanisms: i) Mechanical Interlocking (such as irregularities, porous-microneedles, roughness and physical interpenetration) and ii) Adsorption-Intermolecular chemical bonding (such as amide, Michael addition, nitro, imine, urea and hydrogen bonds, as well as Van de Waals force, electrostatic, *in situ* chain entanglement and biological-inspired).

hydrogel for sealing the incision and measured the bursting pressure (~24 kPa or ~180 mmHg). Moreover, *in vivo* studies in murine models indicated that subcutaneously implanted TA/PEG-SG hydrogel had less fibrosis and more blood vessels formation capacity than the controls (which showed severe structural disorder and acute fibrosis). Furthermore, the animal group treated with this tissue-adhesive hydrogel presented a more accelerated wound healing than the group closed with sutures [90].

With versatile functionality to accomplish biomaterial-tissue integration, wound closure and cell-loaded injectability, Chen et al. developed a highly stretchable tissue-adhesive hydrogel targeting minimally invasive surgeries [91]. The hydrogel was produced by simply mixing a primary covalent polyethylene glycol diacrylate (PEGDA, Mw = 35 kDa) network with a non-covalent network of highly diffusive PEG chains (Mw = 35 kDa). The self-healable tissue-adhesive hydrogel showed adherence to various materials surface (*e.g.*, metals and tissues), as well as higher performance when compared with commercial tissue-adhesives (cyanoacrylate-CA, and fibrin-FB gel). Moreover, the encapsulation of L929 cells suggested that the hydrogel resulted as an interesting platform for cell spheroids generation. This may be interesting for investigation that require model systems to verify the reaching of angiogenesis formation, as well as for cancer tissue model. Apart from that, *in vivo* studies showed that the hydrogel could promote better skin wound healing with lower immune response in comparison to clinical-applied tissue-adhesives [91].

Remarkably, tissue-adhesive hydrogels have been featured with self-therapeutic properties for antibacterial [74] or tissue regeneration finalities [88]. For example, tissue-adhesive hydrogels have self-delivered magnesium ions to promote fibro-cartilaginous interface regeneration [88]. Besides, tissue-adhesive hydrogels have been designed as multi-platform for antibacterial cargo delivery [72]. Also, a thermosensitive bioadhesive hydrogel with reactive oxygen species-eliminating and anti-inflammatory nanoparticles for epidural application was developed to prevent post-laminectomy epidural adhesion by avoiding fibrotic

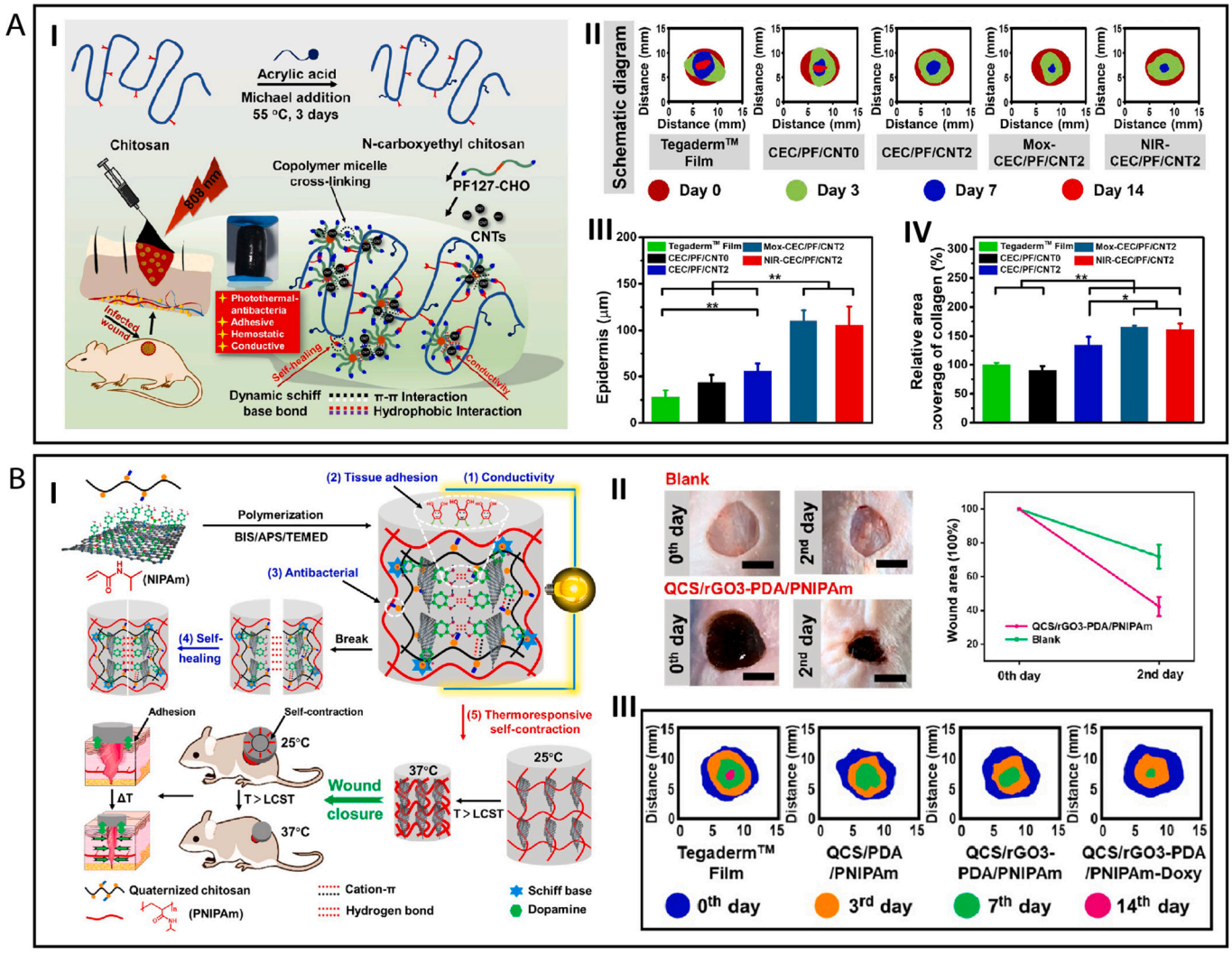



**Fig. 3.** – (A) Nanocomposite hydrogel based on N-carboxyethyl chitosan (CEC) and benzaldehyde-terminated Pluronic F127/carbon nanotubes: (I) Illustration diagram of the hydrogel showing composition and different capabilities. (II) Schematic diagram showing the results from *in vivo* tests, and (III-IV) Quantitative results for contraction area of wounds, the epidermis and the relative area covered of collagen. $^{*}P < 0.05$, $^{**}P < 0.01$ [Reproduced (adapted) from Ref.[75] with permission from Copyright Elsevier] [75]. (B) Scheme of multi-functional conductive hydrogel formed by quaternized chitosan (QCS), polydopamine-coated reduction graphene oxide (rGO-PDA), and poly(N-isopropylacrylamide) (PNIPAm) for wound dressing: (I) Illustration diagram of distinct capability and properties of the hydrogels (conductivity, tissue adhesion, antibacterial, self-healing, thermoreresponsive) and to assist wound closure and healing; (II and III) Qualitative and quantitative results showing that the application of the hydrogel promotes wound closure (scale bar, 5 mm), and (IV) Illustration of the results from *in vivo* tests showing that all hydrogel presented better performance than the control at 14 days post-treatment [Reprinted (adapted) with permission from ref [73], Copyright 2020 American Chemical Society] [73].

formation [72]. In another interesting example, tissue-adhesive hydrogel- was developed with exosomes – a multitherapeutic biological-based nanoparticle – was developed to synergistically treat severe diabetic wounds, by restricting fibrotic formation and stimulating tissue regeneration [32].

### 4.2. Conductive hydrogels (stimuli and monitoring)

The integration of conductive self-healable hydrogels within biological systems is one of the most insightful progress in the biomedical field in this century. Conductive self-healable hydrogels has opened doors for many advances in the healthcare systems [92–94]; either rather by supporting scientists to better transcript and obtain more accurate signals from biological systems and diseases, or by supporting engineers to create translational operational systems to benefit biomedical and healthcare advances. For example, hydrogels have the benefit to provide a better 3D cell-environment; while, their self-healing characteristics can provide a better matrix to mechanically adapt to the cells motion and their conductivity to transliterate the biological signals at cellular level to better develop healthcare technology platforms. Furthermore, the recent emergence of bioconductive biomaterials facilitates releasing of therapeutic signals that elicit biostimulations to tissue repair [95–97].

Interestingly, Baolin Guo et al. evaluated an injectable, degradable and electroactive self-healable hydrogel based on dextran-graft-aniline tetramer-graft-4-formylbenzoic acid and N-carboxyethyl chitosan as a potential candidate of cell-delivery [98]. In another example, stretchable and adhesive-conductive self-healing nanocomposite hydrogels were prepared with NIPAM, laponite and (poly(ethylene glycol)-b-poly (propylene glycol)-b-poly(ethylene glycol) (PF127))/CNTs, Fig. 3A. This hydrogel formulation showed interesting properties including stimuli-responsiveness besides biomedical and human activity monitoring [96]. In another study, an adhesive-conductive self-healing nanocomposite hydrogel was prepared with benzaldehyde-terminated Pluronic F127/carbon nanotubes (PF127/CNT), but instead combined with N-carboxyethyl chitosan (CEC), showing tissue repair properties [75].

Outstandingly, conductive tissue-adhesive self-healable hydrogels with thermoresponsivity self-contraction and therapeutic properties were developed for wound dressings (Fig. 3B). The formulation was based on quaternized chitosan (QCS), polydopamine-coated reduction graphene oxide (rGO-PDA), and poly(N-isopropylacrylamide) (PNIPAm). The formulated hydrogels showed other interesting properties including injectability, anti-oxidation, anti-infection, anti-bacterial, temperature-dependent drug release and biomechanical activity. *In vivo* results showed that these hydrogels significantly improved wound-closure, wound-healing process with high-tissue thickness, collagen disposition and vascularization [73].

Unquestionably, the list of materials employed as conductive biomaterials has extended, for example: metals-like Au, Ag, and Ni; carbon-based, conductive polymers, among others. Regrettably, many of the conductive biomaterials still share an undesirable austere mechanical mismatch with many biological tissues. Thus, studies have been launch to address this problem; for example, Zhang et al. developed a conductive polymer-based hydrogel that mimic natural structures. Their new conductive system was able to improve wound healing, as well as to monitor human body motion [79]. Thanks to the developed conductive polymer-based hydrogel, which had an elastic modulus tuned to match virtually any tissue in the human body -due to the presence of free-catechol groups- the system was able to create an interfacial binding surface by mimicking mussel-like adhesion mechanism [79]. Moreover, Zhang et al. reached this development of a highly stretchable, flexible and conductive (1.16 $S.cm^{-1}$) self-healable hydrogel by simply combining conventional and biocompatible polymers. Besides, their hydrogel displayed thermoresponsive behavior, changing its conductivity according to the applied temperature. Moreover, it also possessed anti-bacterial ability, thus considering it as a potential candidate to treat chronic wounds. In the interim, Wei et al. developed a conductive nanocomposite hydrogel containing glycerol and Laponite® RD to create a hydrogel with anti-freezing properties for biomimetic skin sensors without prejudice regarding temperature [99]. This nanocomposite hydrogels for skin sensor relied on the hypothesis of fully exfoliated clay, in which dissociated $Na^{+}$ ions could resemble the motions of $K^{+}$ ion channels in cell membrane [99]. In other words, the hypothesis is based on voltage-gated ion channel, which is a mechanism resulted by an electrochemical gradient across the cell membrane, due to the changing of ion concentration out/inner cell resulting in charge transmembrane gradient. Altogether, their investigation showed that the conductivity was achieved even at −20 °C, while the system still held elasticity. The latter was evaluated by a finger bending test at different angles: 30, 45, 60 and 90° and at −20 °C. Additionally, conductivity fluctuated from $2.06 \times 10^{-4}$ to $5.48 \times 10^{-4}$ $S.cm^{-1}$ when the temperature was increased from 25 °C to 45 °C; thus showing that the hydrogels have also thermoresponsive properties [99].

### 4.3. Cyborganics

Tissue-cyborganics aim to create a communication and an amalgamation (at micro- & nanoscale) between biomaterials and human body (at tissue and cellular level) to engender undifferentiated interface between humans and machines. Furthermore, this scenario could in real-life codify, respond and transcript with more accuracy signals that could support advances for healthcare technology. By enhancing research-monitoring accurately, where wearable and implantable cyborganic healthcare devices can be created for diagnostics and precision medical treatments, plus supporting the advance for personalized tissue engineering & regenerative medicine in the near future. Recent publications have described the field, addressing limitations and challenges in the cyborganic field [7,100,101]. There are instances of the potential of this novel field of research. For example, Kadumudi et al. developed biomaterials for bionics with applicability in human-motion healthcare monitoring. These biomaterials could be used to assist surgeons to improve surgical movements, as well as monitoring the patient's rehabilitation [102]. Nonetheless, this route of near future for tissue-cyborganics is still at the establishment of a complex construction. Besides of some limitations regarding materials and technologies to better interface the human-machine biointegration, there are also encumbers in terms of biosafety and ethical points.

Meanwhile, materials and technologies have been investigated to support tissue-cyborganics [101,103,104]. For example, Won et al. developed a tissue-adhesive stimuli-responsive electrochemical wireless biosensors for oncological application [103]. Thus, for this purpose, engineering self-healing hydrogel could have an extra bonus by motion-biosensing of distinct cancerous-type tissues, shapes and sizes; consequently, researchers could have a better tool to analyze cancer conditions at real-time *via* bluetooth-connected Smartphone [103]. Therefore, expanding ideas, this approach could be easily protracted to tissue engineering, diseases modelling, and drug discovery. In the interim, in another example, Ge et al. investigated a conductive tissue-adhesive self-healing hydrogel-based sensor for muscle human simulation (Fig. 4B), in order to properly simulating the microstructures and multifunctionalities of human muscle. Those neural networks were allocated in muscle and were able to differentiate gentle touch/heat stimuli and to transfer them into hydrogel, taking advantage of its fiber-reinforced mechanical compliance and thermosensation [104].

The development of materials to support tissue-cyborganics is relatively a newborn field, and external body applications are the most investigated ones [102,105,106]. For example, Kahn et al. developed synergetic supramolecular injectable and conductive tissue-adhesive hydrogels-based sensors by combining polythioctic acid, $Fe^{3+}$ ion, pyromellitic acid and interpenetrating polyaniline. They showed reliable electromechanical performance with high durability (>800 cycles) due to hydrogels' self-healable characteristics [106]. Moreover, their

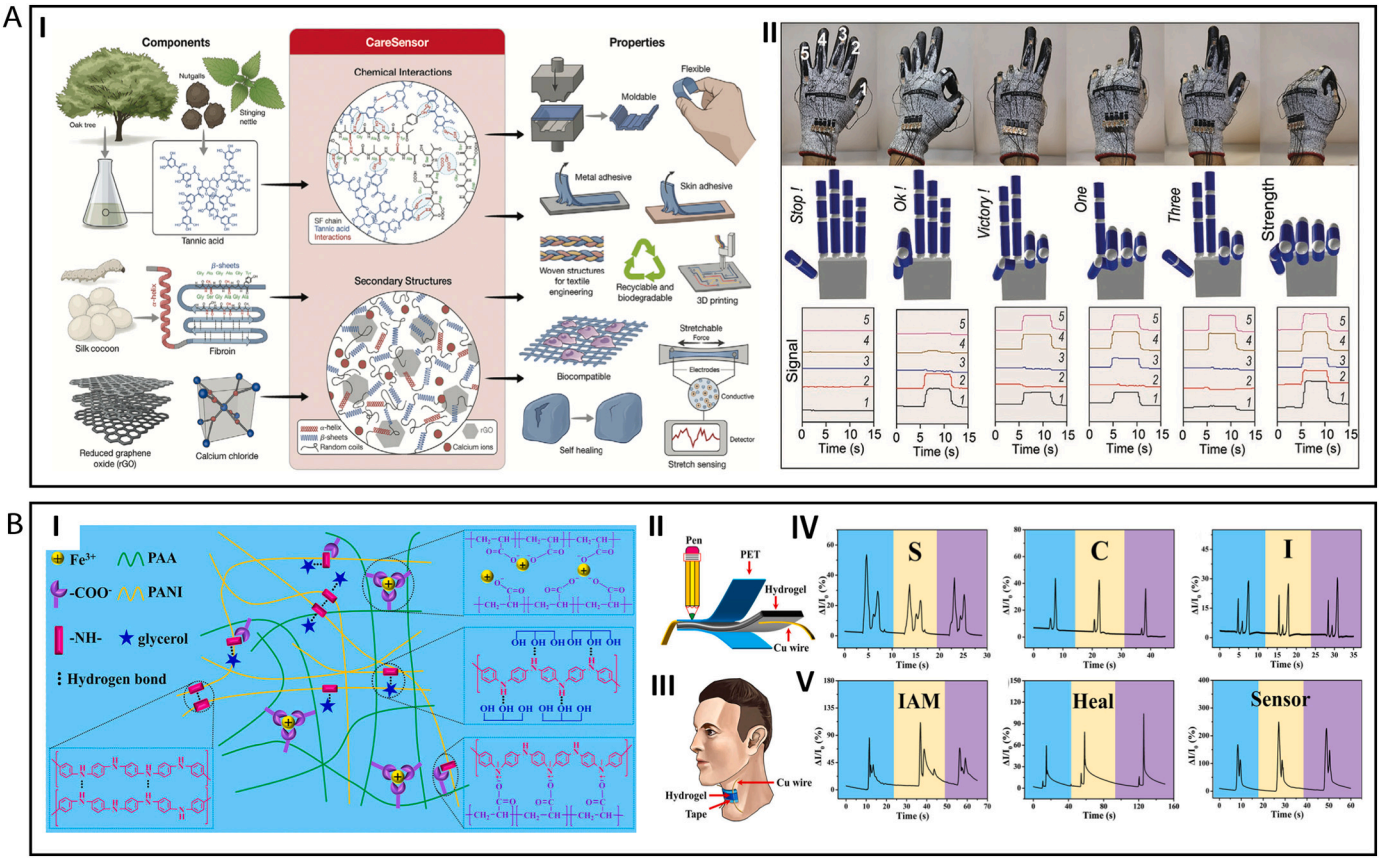



**Fig. 4.** (A) CareGums-named biomaterials: (I) Schematic illustration of the materials and chemical bonds involved in the systems, as well as an overview of their properties and possible applications; (II) It shows various hand gestures monitored with bionic *E*-glove, and corresponding signal responses from CareGums used as flexible electronic. [Reproduced (adapted) from Ref. [102] with permission from Copyright Elsevier] [102]. (B) Hydrogel based on acrylic acid and polyaniline nanofibers: (I) Schematic illustration of the materials and chemical bonds involved in the system; (II-III) Investigation of hydrogels used in flexible-pressure sensing paper-like to detect writings and human motion monitoring, respectively; and, (IV-V) Associated signal responses from these investigations. [Reprinted (adapted) with permission from ref [104], Copyright 2020 American Chemical Society] [104].

hydrogel-based sensor presented high stretchability (>5000 %), ultra-fast self-healability (mechanical recovery in 90 s, electrical recovery of 95 % within 0.7 s) and pressure sensitivity (0.16 $kPa^{-1}$ up to 12 kPa, and 2.8 $kPa^{-1}$ for 16 to 40 kPa) [106]. Additionally, it was possible to achieve detection (response time, 125 ms) comparable to that of human skin, also wearable sensitivity detection of human motion (joint and muscle) [106]. Altogether, the authors claimed that their conductive tissue-adhesive hydrogel-based sensors were potential candidates for conductive 3D printable inks, soft-robotics, artificial intelligence electronic skin (e-skin) and wearable human health monitoring device application.

Nevertheless, studies are ongoing to support tissue-cyborganics visioning intra-body and intra-tissue applications [101,103,107]. For example, Sun et al. developed a self-healable hydrogel with multimodal responsiveness (biosensorial and therapeutic electrostimulation) for wearable and implantable device application [107]. The self-healable conductive hydrogel was obtained with gelatin-difunctionalized (using ureidopyrimidinone/tyramine, UPy/Tyr) combined with PEDOT:PSS-doped (using tyramine, PEDOT:PSS-Tyr); where, the authors conferred the systems as a possible wearable sensors for physiological detection and monitoring by investigating motion sensing, thermal sensing, wireless electrocardiogram (ECG) signals, as well as bioelectrochemistry metabolite sensing and monitoring [107]. Afterwards, they performed *in vivo* rat model studies by applying adhesive conductive self-healable hydrogels to the dura mater on the motor cortex in the right hemisphere of the brain, considering neural recording and therapeutic electrostimulation. Thus, firstly signal waves from 10 Hz to 80 Hz were measured, due to the adhesiveness of the self-healing hydrogels, and the results showed good biomaterial-native tissue integration and signal recordings [107]. Subsequently, therapeutic electrostimulation effect was evaluated by applying *in vivo* epileptic rat model studies and electrocorticography (ECoG) signals were precisely recorded (before, during and after seizure event) [107]. Considering in a clinical future prospect, self-healing hydrogels applied on brain surface could also support medical professionals to circumvent major neuro surgeries and decide the best healthcare treatment for those patients with neuropathological diseases (such as epilepsy, bipolarity, Alzheimer, among others) by applying cyborganic healthcare device with theranostic properties.

Meanwhile, apart from all above publications discussed in this review, still many researchers are also exploring bottom up approaches to support tissue engineering and regenerative medicine progression, *via* studies that can rely in a better reading and interpretation of the human-machine interface. For example, cyborg organoids were studied with synthetic-based nanoelectronic visioning accurate interpretation of spatiotemporal cellular activities in a dynamics cardiac organogenesis [101]. Therefore, substituting synthetic-based material to natural-based conductive self-healing materials, in order to create nanoelectronics for tissue-cyborganics, could further close the spatiotemporal cellular and physiological reading.

In summary, efforts have been made to develop bio-integrated materials and microelectromechanical systems to interface with cells and tissues in order to support biomedical field [97,108–110]. Notably, hydrogels with self-healing, adhesive and conductive properties are of elemental significance for the tissue-cyborganic progression.

## 5. Conclusions & future perspectives

It is well-known that self-healing hydrogels have become important in the field of tissue engineering and regenerative medicine due to their virtue of self-repairing property – thanks to dynamic covalent and non-covalent bonds – where they can better mimic the extracellular matrix milieu. Herein, from the review outcomes, it is possible to comprehend how self-healing hydrogels are a useful asset to act as delivery platforms for different cargos in a multitude of mending tissues, such as bone, cartilage, nerve or skin. Moreover, it is also possible to comprehend that self-healing hydrogels propitiate groundbreaking applications targeting clinical translational setting in surgery and monitoring.

Remarkably, the ability of the self-healing hydrogels to self-repair qualifies them to be explored and applied in minimally invasive medical treatments, for example by injectability process; thus, avoiding major surgery complications and allowing an effective and localized delivery of the cargos, including personalized cells. Moreover, the injectability approach of self-healing hydrogels, in order to treat cartilage-related diseases and regeneration, is a near feasible tactic in clinical future perspective. Considering cartilage a dense tissue that hinders cell-survival, self-healing hydrogels can be used as injectable cell-delivery platform as a tool to overcome drawbacks faced in cartilage-related treatments. Hydrogels have a natural benefit for cell culturing, they endorse an environment with better irrigation of nutrient for the cells. Supplementary, self-healable hydrogels have an extra benefit, they are also able to self-adapt during the injection due to shear-thinning properties; therefore, being less detrimental to cells while being injected, thus preserving the cells viability. Still, in the case of cartilage and also bone tissues, the use of nanotechnology with the employment of nanoclays facilitates the development of nanoengineered-self-healing hydrogels, while conferring outstanding mechanical properties. Moreover, the use of nanoclays can enable osteogenic properties by self-releasing therapeutic ions, which can bring benefits when it comes to future perspectives for osteoporosis treatment and bone tissue regeneration.

Furthermore, injectable self-healing delivery platforms can be functional and advantageous in many other clinical prospects, such as in delicate systems, like nervous systems, with the application of localized cell-delivery therapy to support tissue regeneration and function restoration, since nervous tissue has difficulties of self-repairing. Yet, in a tangible and immediate clinical prospect, self-healing hydrogels, in special those with adhesiveness properties, could similarly be applied in epidural treatment to avoid the drawbacks of epidural fluid leakage, which affects thousands of patient that pass for surgery in need of an epidural anesthesia or lumbar puncture for diagnosis. What is more, the use of adhesive self-healing hydrogels can improve surgical operations as therapeutic sealant and wound closure, while facilitating the adhesion of the biomaterial to the native tissue, reducing surgical operation time, enhancing post-surgery and providing a superior healing process.

On top of everything, the potential of those self-healing hydrogels regarding insights of future prospect applications should be highlighted, for instance the electroconductive self-healing hydrogels. They can better mimic human tissues and can also allow monitoring and sensing of signals from the cells and body responses, thus greasing the wheels for innovative venues to support tissue engineering and regenerative medicine advancement. Hence, this brings in evidence the embryonic area of cyborganics – where machines mingle with human bodies – where self-healing hydrogels may play a key role when designing smart delivery platform systems, which apart from supporting human tissue mending, can likewise improve biomaterials-tissue interface in clinical prospects by also self-detect and self-monitor the progression of diseases and tissue regeneration in real-time. Noticeably, this will strengthen the usage of robotics and computer science knowledge, to support tissue engineering and regenerative medicine, convey it to a new generation stage.

## CRediT authorship contribution statement

**Tatiane Eufrásio-da-Silva:** Writing – original draft, Writing – review & editing, Conceptualization. **Itsasne Erezuma:** Writing – original draft, Conceptualization. **Alireza Dolatshahi-Pirouz:** Writing – review & editing, Conceptualization. **Gorka Orive:** Writing – review & editing, Conceptualization.

## 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.

## Data availability

The authors do not have permission to share data.

## Acknowledgement

We would like to express our appreciation appreciate for the financial support from the Spanish Ministry of Economy, Industry, and Competitiveness (PID2022-139746OB-I00/AEI/10.13039/501100011033) at the University of the Basque Country. Itsasne Erezuma thanks the Basque Government for the Ph.D. grant. Alireza Dolatshahi-Pirouz would also like to acknowledge the Danish Council for Independent Research (Technology and Production Sciences, 8105–00003B), and the VIDI research programme (Project number R0004387), which is (partly) financed by The Netherlands Organisation for Scientific Research (NWO); moreover, as this work has also received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 951747, as well as from Novo Nordisk Foundation under grant agreement No NNF22OC007994. Besides, we would like to thank BioRender.com for the graphic design that we prepared for this work.

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