Materials Today Bio 26 (2024) 101032

Contents lists available at ScienceDirect

Materials Today Bio

journal homepage: www.journals.elsevier.com/materials-today-bio

The application of small intestinal submucosa in tissue regeneration

Yifan Zhao [a,b,1], Hongyi Peng [a,b,c,1], Lingxiang Sun [a,b,1], Jiahui Tong [a,b], Chenying Cui [a,b], Ziyang Bai [a,b], Jingyu Yan [a,b], Danlei Qin [a,b], Yingyu Liu [a,b], Jue Wang [d], Xiuping Wu [a,b,**], Bing Li [a,b,*]

[a] Shanxi Medical University School and Hospital of Stomatology, Taiyuan, 030001, Shanxi, China
[b] Shanxi Province Key Laboratory of Oral Diseases Prevention and New Materials, Taiyuan, 030001, Shanxi, China
[c] Academy of Medical Sciences, Shanxi Medical University, Taiyuan, 030001, Shanxi, China
[d] The First Hospital of Shanxi Medical University, Taiyuan, 030001, Shanxi, China

ARTICLE INFO

Keywords:
Small intestinal submucosa
Tissue engineering
Decellularized extracellular matrix
Regenerative medicine

ABSTRACT

The distinctive three-dimensional architecture, biological functionality, minimal immunogenicity, and inherent biodegradability of small intestinal submucosa extracellular matrix materials have attracted considerable interest and found wide-ranging applications in the domain of tissue regeneration engineering. This article presents a comprehensive examination of the structure and role of small intestinal submucosa, delving into diverse preparation techniques and classifications. Additionally, it proposes approaches for evaluating and modifying SIS scaffolds. Moreover, the advancements of SIS in the regeneration of skin, bone, heart valves, blood vessels, bladder, uterus, and urethra are thoroughly explored, accompanied by their respective future prospects. Consequently, this review enhances our understanding of the applications of SIS in tissue and organ repair and keeps researchers up-to-date with the latest research advancements in this area.

1. Introduction

Most conventional methods for tissue regeneration depend on tissue transplantation; however, autologous and allogeneic transplantation have their limitations [1]. Autologous transplantation can result in complications such as discomfort, infection, and formation of scars, whereas allogeneic transplantation is linked to an increased likelihood of immune rejection and transmission of disease [2,3]. These circumstances further highlight the need for biological alternatives, which are already being developed in the fields of medical regeneration and tissue engineering [4].

Tissue engineering is an interdisciplinary field that integrates concepts from both engineering and life sciences to develop biomaterials that can serve as biological substitutes for damaged or lost tissues, with the aim of enhancing, preserving, or repairing their function [5]. The tissue engineering triad consists of cells, scaffolds, and growth factors [6]. These three elements interact to renew, regenerate, and replace parts or whole tissue structures. The interface between cells and scaffold materials comprises a complex and dynamic microenvironment. Cells impact their surroundings via cytokine secretion, while the intrinsic properties of the scaffold material can alter cell fate [7]. Additionally, scaffold materials can also release degradation by-products, which are capable of influencing the shape and traction of cells by providing new signals [7–9]. Therefore, the pursuit of an optimal biomaterial scaffold is a crucial part of tissue regeneration.

Typically, tissue engineering scaffolds are commonly fabricated using three biomaterials: ceramics, synthetic polymers, and natural polymers [6]. Ceramic scaffolds, such as hydroxyapatite, find extensive application in bone tissue regeneration because of their exceptional mechanical strength and structural resemblance to natural minerals. However, their clinical applications in tissue engineering are restricted due to their brittle nature and difficulty in implantation [10]. Synthetic polymers include polylactide (PLA), polylactic-glycolic acid (PLGA), polycaprolactone (PCL), polysebacate glycerides, and polyurethane (PU) with controlled porosity and size that can be manufactured with custom structures [11]. However, they are susceptible to fibrotic, infectious, and inflammatory reactions in the surrounding population [12]. Natural polymers, such as gelatin, chitosan, collagen, and

* Corresponding author. Shanxi Medical University School and Hospital of Stomatology, Taiyuan, 030001, Shanxi, China.
** Corresponding author. Shanxi Medical University School and Hospital of Stomatology, Taiyuan, 030001, Shanxi, China.
E-mail addresses: 77wxp@163.com (X. Wu), libing1975vip@163.com (B. Li).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.mtbio.2024.101032
Received 13 December 2023; Received in revised form 4 March 2024; Accepted 15 March 2024
Available online 18 March 2024

hyaluronic acid, have gained increasing attention in various fields due to their biocompatibility, degradability, and non-toxicity [13]. Nevertheless, the rapid degradation of these materials and the limited availability of bioactive factors are major challenges.

Given the specific merits and drawbacks associated with the aforementioned biomaterials, it is noteworthy that acellular tissue-derived extracellular matrix (ECM) bioscaffolds possess significant potential in fostering beneficial and practical tissue remodeling in diverse clinical contexts [14]. In addition to good biocompatibility and low immunogenicity, ECM also has a biomimetic three-dimensional network environment [15]. This network forms a microenvironment for cells, which aids in homeostasis, tissue formation, and repair [16]. Small intestinal submucosa (SIS) is a naturally occurring ECM that possesses a biomimetic three-dimensional microenvironment suitable for cellular growth as well as the capacity for continuous and dynamic tissue repair [17]. As a result, SIS has garnered substantial attention in the field of tissue regeneration.

SIS was first used more than 50 years ago when it was used as an autologous alternative to the superior and inferior vena cava in dogs [18]. This paved the way for using SIS as a biological scaffold to regenerate tissue. In 1992 an experiment was carried out by G. E. Sandusky, in which a vascular graft of small diameter, derived from the porcine small intestine submucosa, was implanted in the carotid artery of a canine. The implantation has been compared to an autologous saphenous graft, which is implanted into the opposite carotid artery [19]. The study found no statistically significant difference. Since then, SIS grafts have been intensively studied in skin, abdominal wall, bladder and tendon areas [20–24]. In addition, SIS has been approved by the U. S. Food and Drug Administration and is being used in clinical settings to repair various forms of tissue damage. Today, the applications of SIS in tissue engineering have been further extended to include bone regeneration, reproductive system, valve replacement, tympanic membrane repair, meniscus, vocal cords, trachea, etc [25–31].

In recent years, numerous studies have emerged on the application of SIS, including optimizing decellularization protocols, finding better cross-linking materials, and using functionalized SIS for tissue and organ repair. This literature review covers the previous five years of SIS research. Topics discussed included the composition, characteristics, preparation, classification, and advanced techniques of SIS, as well as examples of its applications in various tissues and organs. We conclude with a summary of outstanding issues in the field of SIS and potential future applications in tissue engineering. The application and composition of functional decellularized SIS to tissue regeneration is schematically illustrated in Fig. 1.

2. Overview of SIS

2.1. SIS description and fabrication

SIS is a biomaterial derived from the intestines of animals (most commonly pigs, cattle, sheep) and has been used in a variety of medical applications. It is a thin, translucent graft (0.1 mm wall thickness) obtained by mechanical removal of the mucosa, serous membrane, and muscle membrane of the small intestine by physical methods [32]. The SIS exhibits a pale white and translucent appearance with a thickness measuring approximately 80–100 μm. The mucosal layer is smooth in texture, whereas the muscular layer presents a rough texture [33]. Scanning electron microscopy revealed that the SIS has a complex porous microstructure, with bundles of collagen fibers forming both mucous and muscular layers. The mucous side appears denser and smoother than the serous side.

The preparation of decellularized SIS involves multiple steps, such as mechanical dissociation, degreasing, enzymatic digestion, detergent treatment, freeze-drying, and irradiation sterilization [34]. The purpose of immersing the physically treated SIS in a series of chemical solutions is to remove the cells. Decellularization is critical in preventing adverse inflammatory reactions and immune rejection after implantation. Over the last two decades, researchers have developed numerous techniques to obtain a decellularized ECM while preserving its mechanical integrity, biological activity, biochemical composition, and three-dimensional structure, as well as reducing immunogenicity [35]. Common methods of decellularization include physical methods (temperature, pressure), chemical methods (acid-base, hyper-hypotonic, detergents), and biological methods (enzymes) [36]. Meanwhile, the efficiency criteria for decellularization comprise three main aspects: (1) the dry weight of double-stranded DNA per milligram of ECM must not exceed 50 ng, (2) the length of the DNA fragments should be below 200 base pairs, and (3) there should be no detectable nuclear material in tissue sections stained with DAPI or H&E [36].

Yanhui Ji assessed three distinct SIS decellularization methods: Abraham's methods, Luo's methods, and Badylak's methods [37]. The brief procedures are shown in Table 1. The SIS produced using three distinct techniques exhibited excellent biocompatibility and a successful decellularization process. However, regardless of the decellularization

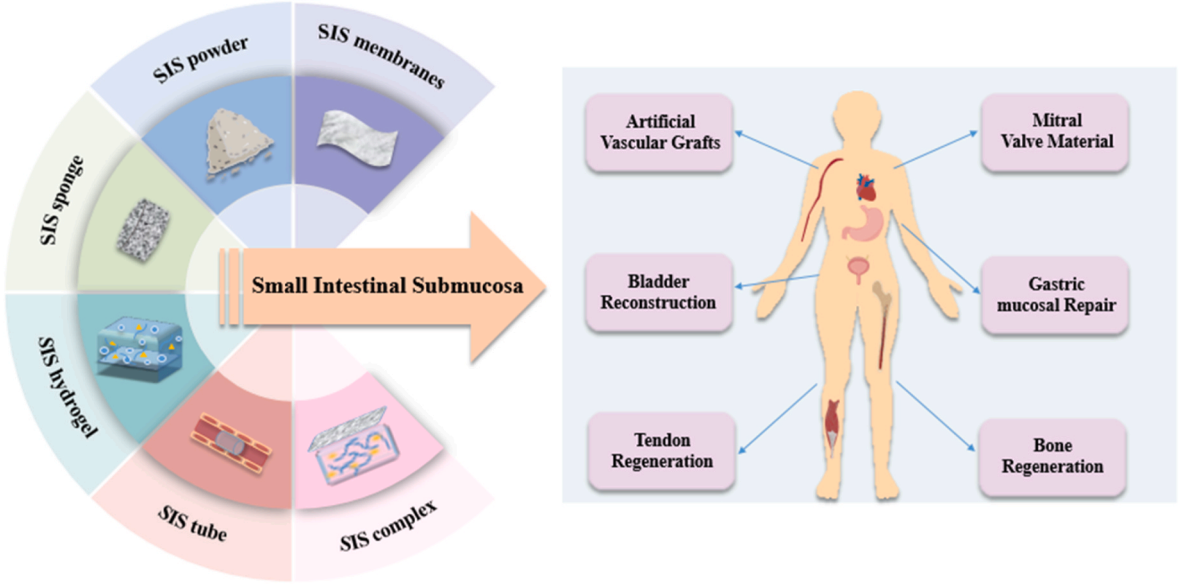

Fig. 1. Schematic illustration of a functional decellularized SIS for tissue regeneration.

Table 1

Preparation method	Physical methods	Chemical methods
Native SIS material	Remove the mucous membrane, the entire muscular layer of the adventitia, and the serous membrane in layers by mechanical layering and wash with water	No other chemicals.
Badylak's method	Same as native SIS material	0.1% peracetic acid (PAA) , phosphate-buffered saline (PBS) , deionized water.
Abraham's method	Same as native SIS material	EDTA and NaOH solution, HCl and NaCl solution, NaCl and PBS, sterile water.
Luo's method	Same as native SIS material	methanol and chloroform, EDTA, sodium dodecyl sulfate (SDS), peracetic acid and 20% ethanol.

method employed, the microstructural integrity and bioactive constituents of the prepared SIS are degraded to varying extents. In recent years, researchers have developed a new decellularization process for SIS. This method utilizes the mild detergent Tergitol as a replacement for the toxic Triton X-100. Quantification based on quantum bit fluorescence revealed that the concentration of decellularised SIS DNA was 12.28 ± 3.94 ng DNA/mg dry tissue, which is lower than the 50 ng/mg dry tissue threshold set by Crapo et al. [36]. Moreover, a two-photon analysis conducted during histological examination verified the presence of collagen fibers in decellularized SIS. The conservation of ECM was verified by overlapping decellularized SIS and natural SIS spectra, identifying shared peaks related to collagen type I, type IV, and type V [38]. The optimized protocol effectively removes cells and DNA from SIS while preserving the extracellular matrix. In addition, Tiziana Palmosi's utilization of Tergitol 15 S 9 as a substitute for Triton X-100 has demonstrated superior efficacy in decellularization [39]. The study finds equivalent decellularisation efficacy and retention of extracellular matrix between Tergitol 15 S 9 and Triton X-100. However, it is worth noting the disorganized and disrupted collagen fibers observed with Triton X-100, while the fibers appeared to be slightly thinner with Triton X-100 in the SEM, without collapsing the ECM. Furthermore, the tissue treated with Triton X-100 demonstrated a significant increase in resistance and stiffness values compared to the use of Tergitol 15 S 9, which did not affect tissue mechanics and maintained comparable values for the same parameters as natural tissue [39]. Still, there is potential for further development in the creation of a new, gentle decellularization technique.

2.2. SIS superiority and limitations

First, decellularized SIS biomaterials have excellent biocompatibility. The main constituents of SIS include collagen, elastin, proteoglycans, glycosaminoglycans (GAGs), and adhesion molecules [40]. The predominant collagen types found in SIS are type I and type III [41], with the collagen component accounting for approximately 90% of its dry weight [42]. Collagen plays an important role in facilitating epithelialization by promoting keratinocyte migration and containing von Willebrand factor binding domains that help regulate bone morphogenetic proteins and promote vascular development [43,44]. SIS also contains several GAGs, including heparin, hyaluronan, chondroitin sulfate A, and keratan sulfate, as well as adhesion molecules such as fibronectin and laminin [45]. In addition to these components, SIS also contains important growth factors (GFs) such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF-2), and transforming growth factor β (TGF-β) [46]. These GFs remain biologically active even after acetic acid/ethanol sterilization and long-term storage at 4 °C [47]. They bind to proteins and are gradually released as the SIS degrades, stimulating and regulating proliferation and differentiation involved in cell migration, tissue regeneration, remodeling, and angiogenesis [48]. Several types of stem cells, including mesenchymal stem cells such as umbilical cord (UC-MSCs), human bone marrow-derived (hBMMSCs), urine-derived (USCs), tendon-derived (TDSCs), adipose-derived (ADSCs), and genital mesenchymal (GMSCs) stem cells were cultured on SIS without additional compounds or substrates. All cells exhibited robust growth and proliferation, indicating that SIS is a viable substrate for stem cell culture.

Second, Stephen F. Badylak has explored the immunogenicity of SIS [49]. Oligosaccharide-Gal (Gal1,3-Gal 1–4GlcNAc-R) is a cell surface molecule present in most species that can cause immune rejection after organ xenotransplantation. However, humans typically do not express Gal epitopes and produce large amounts of anti-Gal antibodies [50]. T B McPherson has found the presence of Gal epitopes in SIS [51]. To study in detail the potential role of Gal epitopes in SIS immune recognition, Roberta H Raeder and colleagues implanted SIS into mice (Gal −/− mice) with a knockout of the 1,3-galactosyltransferase gene [52]. The results showed that although SIS remodeling and inflammation were prolonged in the α gal(−/−) mouse group compared to the α gal (+/+) mouse group, they disappeared by day 35. It was concluded that anti--α-gal antibodies do not affect the ability of xenoextracellular matrices to serve as biological scaffolds for tissue remodeling. In another study, xenogeneic tissue, homologous tissue, or SIS was implanted under the skin of mice, and histological analysis of the transplant site was performed to confirm the rejection of SIS [53]. Xenografts exhibit a strong inflammatory response on day 1 of implantation, consisting mainly of polymorphonuclear leukocytes (PMNs). Day 10 showed a chronic inflammatory response, mainly neutrophils and T cells. By day 28, the inflammatory process within the implant and at the surrounding interface between the implant and the host tissue worsened dramatically. However, the homograft and SIS showed consistent responses. Day 1 showed an acute inflammatory response, and day 10 showed a minimal inflammatory response, consisting mainly of monocytes. By day 28, the remodeling response was almost complete. SIS did not produce acquired adverse immune responses in mice.

Lastly, the resorbability of SIS is important for repairing damaged or missing tissues. Thomas W. Gilbert et al. used isotope ^{14}C to label SIS and explore the degradation process of SIS by collecting metabolic organs, blood, urine, and feces [54]. The study found that SIS degraded rapidly after implantation, with 40–60% degradation within 4 weeks. The degraded SIS scaffold is involved in the tissue remodeling process and is replaced by new ECMs deposited by cells. ^{14}C was undetectable at 60 days for the Achilles tendon and 90 days for the bladder [55,56].

Although SIS holds promising potential, the reagents and decellularization methods used in its preparation can disrupt the natural tissue structure, leading to reduced mechanical performance [57]. In their study, Cadena et al. investigated the tensile mechanical properties of SIS scaffolds and found that the 4-layer scaffold exhibited significantly higher maximum load compared to the single-layer and double-layer scaffolds. Additionally, the longitudinal load capacity along the intestinal axis was higher than the transverse load capacity [58]. Moreover, SIS itself does not possess strong antibacterial properties, which is a key factor in delayed wound healing caused by bacterial infection [59]. To address this, Zelong Song et al. developed a novel wound dressing (SIS/ZIF) by combining a zinc zeolite imidazole ester scaffold with SIS membrane. The SIS/ZIF dressing demonstrated sustained release of Zn2, which activated the hypoxia-inducible factor α (HIF-α) pathway and enhanced tissue regeneration, as proven through in vitro experiments and in vivo infectious wound models [60]. Limited anticoagulant activity is another drawback of SIS [61,62]. Therefore, further research is needed to modify this ECM material and expand its application areas.

ECM derived from humans and animals is widely used in tissue regeneration engineering. Among the representative biomaterials, acellular dermal matrix (ADM), acellular amniotic membrane (AAM), and SIS are commonly used [57]. To examine their differences in

material properties including physical properties, biodegradability, and immune response performance, we will embark on further exploration. ADM, derived from human or animal skin, is primarily used for treating skin wounds [63]. AAM, which lacks epithelial cells, consists mainly of collagen, elastin, laminin, and fibronectin. It provides a conducive environment for cell proliferation and differentiation [64]. In comparison to ADM, SIS exhibits lower strength and toughness, indicating inferior physical properties [65]. However, SIS has higher water vapor transmission rate and superior water absorption performance than ADM [65,66]. All three materials, ADM, AAM, and SIS, display degradation properties [67]. Nonetheless, ADM degrades at a slower rate than SIS, and some studies suggest that it is not degraded but rather assimilated by patient cells and growth factors, thereby facilitating angiogenesis and dermal regeneration [68–70]. Additionally, both AAM and SIS generate antimicrobial substances during the degradation process, which contributes to their antibacterial capability [71,72]. Regarding immunogenicity, although the precise mechanism by which ADM mitigates chronic fibrosis is not yet fully understood, animal studies have shown its biomimetic properties in reducing periprosthetic inflammation and enhancing host cell integration [73]. Furthermore, research has indicated that AAM not only minimizes immune rejection of implanted membranes compared to intact amniotic membrane but also enhances cell attachment and differentiation through the retained collagen [74].

2.3. Sterilization and preservation

Efficient sterilization is a crucial preliminary step in tissue engineering to remove any existing genetic material, along with residual bacterial and viral components, thus minimizing the risks of immune responses [75]. Furthermore, implementing appropriate preservation techniques is vital in maintaining the three-dimensional structure and bioactive elements of the ECM [76]. Currently, common sterilization and preservation methods for decellularized SIS scaffolds include peracetic acid (PAA) disinfection, lyophilization, and ethylene oxide (EO) sterilization. Research has indicated that FGF-2 and TGFβ1 bioactivity remains intact in SIS post PAA disinfection and EO sterilization, likely due to their strong bindings with structural proteins and proteoglycans [77]. Moreover, PAA treatment does not diminish the quantity of fibronectin and HA, while lyophilized storage does not impact the matrix structure of SIS. In vitro studies have demonstrated that PAA disinfection, lyophilization, and ethylene oxide sterilization promote fibroblast adhesion, induce PC12 cell differentiation, and enhance VEGF secretion in fibroblasts on treated SIS scaffolds [78].

2.4. SIS scaffold

We can obtain initial SIS membranes with the previous preparation methods and utilize a variety of methods to produce other SIS scaffolds (e.g., SIS hydrogels, SIS sponges, SIS tubes, and SIS complexes). This not only enhances the material variety of SIS but also generates novel concepts for applying SIS across diverse tissues and organs. SIS membranes is the most basic form, and it has always been a research hotspot in the repair of skin tissue defects. In recent years, SIS membranes have been increasingly used for bladder reconstruction, uterine repair, and vaginal repair. Furthermore, the frozen dry SIS is crushed using a cryogenic crusher and sieved through a 200-mesh screen to obtain SIS powder [79]. SIS powder is added to polymethyl methacrylate (PMMA) to create partially degradable bone cement. Compared with the PMMA sample, the elastic modulus of SIS-PMMA bone cement is closer to the range of human cancellous bone (50–800 MPa) (Fig. 3C). SIS hydrogels are considered promising candidates for tissue repair due to their ability to provide a moist environment during the healing process, good permeability, and absorption [80]. Additionally, SIS hydrogels possess drug loading and sustained drug release capabilities [81]. SIS tubular scaffolds offer potential benefits in tissue engineering for the creation of biologically active small blood vessels [82]. Applications of SIS in the fabrication of various biocomposites have also been extensively explored.

With the development of electrospinning scaffold fabrication techniques, advanced SIS scaffolds with improved properties have emerged in tissue regeneration. In recent years, the combination of SIS and PLGA has been used in the repair of bones, tendons, and esophagus using electrospinning technology [83–85]. In addition, Min Ju Kim et al. prepared a bilayer SIS/PCLA scaffold (inner SIS/PCLA tablet and outer PCLA tablet) containing 11 amino acid long neuropeptide substance P (SP) as a cell-free scaffold to stimulate wound healing by mobilizing human mesenchymal stem cells [86]. The contact angles of PCLA and SIS/PCLA sheets are about 97° and 51°, respectively, so the SIS/PCLA sheet as the inner layer is more hydrophilic, and the PCLA sheet as the outer layer is more hydrophobic. *In vitro* experiments showed that 42% of SP was released after 12 h, 51% after 24 h, and about 99% after 21 days. SIS/PCLA and SP-loaded SIS/PCLA sheet were implanted on the left and right sides of nude mice, respectively, and ICG-labeled hMSCs were injected into the tail vein to study their in vivo recruitment capacity. A pronounced pink color is observed in the wound after 1 h on the side of the SP-loaded SIS/PCLA sheet, which increases over 1 day and then gradually decreases, in 2 days in the wound itself and 4–10 days in the peri-wound area. The results of the studies showed the ability of SP-loaded SIS/PCLA sheet to recruit cells and promote wound healing. Furthermore, coaxial electrospinning technology was also used to create a bionic periosteum consisting of a shell made of SIS and a nucleus made of PCL [87]. The fibers of the biomimetic periosteum are arranged in parallel and have a distinct core-shell structure. Biomimetic periosteum was co-cultured with HUVECs, Schwann cells, and BMSCs, and compared with the PCL group, the PCL-SIS group significantly promoted cell proliferation and migration. The results of in vivo experiments showed that the collagen in the PCL-SIS group was significantly larger than that in the PCL group.

3D bioprinting is widely used due to its unprecedented efficiency in mimicking 3D microarchitectures. Liang Yang and his colleagues utilized extrusion low-temperature 3D printing to construct a new biomimetic scaffold composed of SIS-ECM and Sr2/Fe3 co-substituted hydroxyapatite (SrFeHA) [88]. The results showed that the mechanical strength (Young's modulus) of the composite scaffold is significantly higher than that of pure SIS due to the increase of HA particles. In the dry or wet state (immersed in media) composite scaffolds still retain their 3D porous structure, and their average pore size (313.3–379.2 μm) and porosity (74.8–81.4%) allow new blood vessels/bones to grow inward. In contrast to the linear accelerated degradation of pure SIS scaffolds, composite scaffolds exhibit a relatively delayed degradation rate due to the formation of mineralized apatite crystals. Soaking it in neutral PBS (PH 7.4) for 20 days degraded by about 17.6%. *In vitro* experiments showed that the scaffold had a strong support effect on the proliferation and functional development of HUVECs and MC3T3 osteoblasts without cytotoxicity, confirming the excellent biological activity and biocompatibility of cryogenic printing scaffolds. The results of RNA sequencing showed that the Amot gene was significantly up-regulated and the YAP/TAZ gene was down-regulated in SIS/SrFeHA compared with SIS, so the main mechanism of angiogenesis induced by SIS/SrFeHA was considered to be the Amot+/YAP−/Hippo signaling pathway [88]. Additionally, Yiqiang Hu and colleagues have developed a low-temperature 3D printing technology that combines SIS, mesoporous bioactive glass (MBG), and exosomes to create 3D stent dressings (SIS/MBG@Exos) [89]. The hydrogel scaffold SIS/MBG@Exos not only continuously releases bioactive exosomes derived from BMSCs, but also promotes the proliferation, migration, and vascularization potential of HUVECs. The results of animal experiments showed that the SIS/MBG@Exos hydrogel scaffold increased blood perfusion in wounds, shortened wound length, and promoted collagen deposition.

3. SIS modification

3.1. Physical methods

A common approach to enhance the mechanical properties of SIS membranes is to increase the number of layers of the SIS membrane. In a study of SIS membranes as guide bone regeneration (GBR) membranes for peri-implant dehiscence defects in beagle dogs, the 8-layer cell-free SIS membrane not only had superior mechanical properties over collagen membranes when wet, but also exhibited collagen membrane-like ways to enhance bone regeneration of peri-implant defects [90]. In another study, 2- and 4-layer SIS membranes were used as tissue-engineered heart valves for valve replacement in juvenile non-human primates. To simulate pediatric mitral valve function at 6 weeks, the SIS membrane is subjected to a fatigue test. The results showed that the %RF of the 4-layer and 2-layer mitral valves was significantly higher compared to the bioprosthetic valves ($p < 0.05$), which can be attributed to the unique strain hardening phenomenon that occurred on the 2-layer PSIS material under cyclic fatigue loading conditions, resulting in leaf hardening. Compared to the non-fatigued 2-layer, 4-layer, and fatigued 4-layer specimens, the fatigued 2-layer PSIS exhibited a significantly higher yield stress ($p < 0.05$) and a slightly more significant yield strain ($p = 0.06$) [91]. Bowen Li and colleagues prepared asymmetric SIS membranes by cryo-cross-linking. The decellularized SIS is first ground to a powder by a cryo-grinder, lyophilized using a cryo-dryer to form a SIS sponge, and then bonded to a dense SIS membrane to create an asymmetric membrane. Asymmetric SIS membranes have higher porosity, significantly reduced contact angle, and higher wetting tensile strength compared to conventional SIS dense films, possibly due to cross-linking or bonding of the interface with highly concentrated SIS solutions. However, asymmetric SIS membranes degrade slightly faster than dense SIS membranes, likely due to their better wettability and higher specific surface area [92]. Layer-by-layer (LbL) assembly and coating of SIS membranes with biomaterials is also a physical method for modifying SIS membranes. Bi et al. modified the SIS membrane by layer-by-layer assembly of silk fibroin (SF). Compared with the SIS group, SF-functionalized SIS membranes have higher mechanical properties and lower degradation rates. There are two reasons for this, one is the high mechanical strength of the SF itself, and the other is the β-fold structure formed by the SF on the surface. The β lamellar structure of SF makes the SIS surface more hydrophobic and has a protective effect on degradation, and this SF protein with a β-fold structure fills the SIS network and easily interacts with SIS proteins such as hydrogen bonds, thereby enhancing the physical cross-linking of SIS [93]. Lu Wang and his colleagues have designed o-nitrobenzene-modified gelatin coated with acellular submucosal (GelNB@SIS) composite hydrogels for the repair of skin lesions. Under ultraviolet irradiation, the GelNB@SIS benzyl alcohol structure is converted into a benzaldehyde structure, which interacts with the amino group of the tissue and improves its adhesion strength [94].

3.2. Chemical methods

Polyphenols, found in many plants and marine organisms, are a class of compounds consisting of two or more phenolic building blocks [95]. It is very convenient to control the physicochemical and biological properties of biomaterials because the distinct chemical structure of polyphenol materials (catechols, resorcinols, hydroglucinols, and hydroxyquinoline groups) can react with different molecules through covalent and non-covalent interactions [96]. The phenolic hydroxyl group of the polyphenol material can form hydrophobic bonds and hydrogen bonds with the proteins of the SIS scaffold, thereby improving the mechanical properties of the scaffold [97]. In recent years, polyphenolic compounds such as proanthocyanidins, quercetin, and genipine have been widely explored for SIS scaffold modification [98–100]. In one study, tannic acid (TA) was added to SIS hydrogels to prepare a novel composite hydrogel [80]. There was no significant difference in porosity and pore size compared to the original SIS hydrogel. However, due to the abundant hydrogen bonds of TA, a three-dimensional cross-linking network can be formed inside the hydrogel, thereby enhancing the stability of the scaffold. In addition, the swelling rate of TA-SIS hydrogels has increased due to TA-induced cross-linking between water molecules and the SIS hydrogel matrix, which favors the absorption of tissue exudate and maintains a moist healing environment. NIH-3T3 cells seeded onto hydrogels exhibit a regular spherical morphology, with little observable cell debris. In another study, the curcumin-SIS hydrogel showed sufficient interconnected porous structure, with porosity (87–94%) and pore size (50–357 μm) meeting the criteria for suitability for tissue regeneration scaffolds [81]. Due to the hydrophobicity of curcumin, the water-holding capacity of curcumin incorporated into SIS hydrogels is gradually reduced compared to pure SIS hydrogels, but in general, the fabricated scaffolds are hydrophilic in nature. In addition, due to the high degradation of curcumin and the effect of curcumin particle dispersion, the degradation rate of curcumin-SIS hydrogel increased with the increase of curcumin content.

3.3. Biological methods

Recellularized scaffolds are structures that receive implanted stem cells, chondrocytes, and epithelial cells to provide both form and function [101]. Successful treatment of full-thickness skin defects in small animal models using bone marrow mesenchymal stem cells and acellular bovine SIS [102]. Mesenchymal stem cells can differentiate into a range of cell types and exhibit exceptional efficacy in tissue engineering applications, including endometriosis, hemimembrane disease, regeneration of taste buds, regeneration of the bladder, regeneration of the Achilles tendon, and healing of skin wounds [103–106]. Due to its biological and physical properties, SIS is deemed a desirable biological scaffold for applying MSCs in tissue repair. In recent years, considerable research has been conducted on the use of cell-free strategies for repairing damaged tissue. These strategies involve inducing cell activation and accumulation at the site of damage by utilizing appropriate stimulation and recruitment factors, as well as recruiting endogenous stem cells to the site of the damage [107].

In addition to seeding cells on SIS scaffolds, seeding growth factors on SIS scaffolds is also an excellent modification method. Heparin and VEGF modified SIS small vessel grafts have been successfully manufactured and implanted into the arterial system of newborn lambs. After 6 months of implantation, the implant site matches the growth of the contralateral autologous carotid artery and matures into the native artery [82]. Secretory Klotho (SKL) and heparin were cross-linked with SIS to prepare tissue-engineered bioactive small vessels and functionalized SIS small vessels promoted the adhesion and proliferation of endothelial cells by up-regulating the expression of RhoA and Rac1 in endothelial cells. Shows an increase in patency rate, endothelialization, and smooth muscle regeneration in a rabbit carotid model [108].

4. Tissue repair using functional SIS

4.1. Skin repair

The skin, comprising the epidermis, dermis, and subcutaneous tissue, is the largest organ system in the human body. It encompasses various structures, including sweat glands, sebaceous glands, hair, blood vessels, lymphatic vessels, and muscle fibers [109]. It performs a variety of roles, including sensing, metabolism, immunological response, temperature regulation, and other functions to maintain homeostasis and physiological processes [110]. It also serves as a tangible hindrance to external intrusions in its surroundings.

Burns and other common skin injuries, as well as chronic and acute wounds, substantially decrease mobility and quality of life [111]. Even though research on biological scaffold materials has been active,

inadequate vascularization is one of the major obstacles to effective skin restoration [112]. A recently discovered promising technique for skin regeneration is the production of biologically decellularized SIS. For example, a team of researchers discovered that the SIS membrane modified with proangiogenic oligopeptide (QSHGPS) can encourage angiogenesis and repair of critical-sized full-thickness wounds on the skin [113]. As collagen is the primary component of the SIS membrane, scientists construct chimeric peptides utilizing the collagen-binding peptide sequence TKTLRT and the pro-angiogenic oligopeptide sequence QSHGPS. This process achieves SIS membranes loaded with specific oligopeptides. In umbilical vein endothelial cells, the chimeric peptide-modified SIS membrane (SIS-L-CP) significantly promotes the expression of angiogenesis-related factors. Similarly, small extracellular vesicles (sEVs) bind to porcine intestinal submucosa-derived hydrogel materials (SC-ps-sEVs) via peptides that have a strong ability to promote angiogenesis and effectively heal full-thickness dermal wounds in diabetic rat models (Fig. 2A) [114].

In addition, an important reason for the persistence of chronic wounds is the persistent inflammatory response. The mineral bitumen (MP) is loaded in the acellular ovine small intestine submucosa (AOSIS) and endowed with anti-inflammatory functions [119]. The IL-10 serum level was elevated and the TNF-a level was decreased in the treated groups compared to the control groups. Moreover, open wounds are vulnerable to bacterial infections when exposed to the environment. To address this issue, a recent study developed a novel approach that combines photothermal (PTT)/chemodynamic therapy (CDT). This method involves the simultaneous assembly of black phosphorus nanoparticles (BPNs), polydopamine (PDA), and silver nanoparticles (Ag NPs) to construct the BPNs-PDA@Ag nanosystem (Fig. 2B) [115]. The nanosystem is integrated into porous dSIS-ECM, resulting in the creation of a three-dimensional bioactive composite scaffold known as dSIS-BPNs-PDA@Ag. The scaffold shows a broad-spectrum bactericidal effect (more than 99.6%) against both *E. coli* and *Staphylococcus aureus*. In another study, Yi Wang and colleagues utilized 2-methacryloyloxyethyl phosphorylcholine (MPC) to chemically modify the SIS, which is rich in vascularized bioactive factors, to confer its antifouling ability for the treatment of SD diabetic rat skin defect models (Fig. 2C) [116]. Immunohistochemical staining revealed that the SIS-MPC biopsy demonstrated superior bacterial anti-adhesion properties (100 times more resistant to staining than commercial patches), while also promoting fibroblast growth and collagen formation. This was attributed to accelerated vascularization and inflammatory regulation mediated by the TGF-β and MAPK pathways. Furthermore, XiaoYa Chen Liang Yang et al. reports on a new mechanically active hydrogel dressing (SIS-P-NIPAm hydrogel). This dressing is based on SIS and the heat-responsive polymer PNIPAm [120]. Adding a coupling agent enables effective adhesion of the SIS-PNIPAm hydrogel to the skin and its spontaneous contraction at body temperature is conducive to wound healing. Such SIS-PNIPAm hydrogels have excellent biocompatibility, and they enhance vascularization and modulate macrophage polarization for promoting wound healing.

4.2. Bone regeneration

Bone is a vascularized tissue that can undergo remodeling and recovery following minor injuries. Nevertheless, the potential for reshaping bone defects arising from severe trauma, tumors, and osteoarthritis is restricted [121]. In recent decades, researchers have developed bone graft materials utilizing both synthetic and natural alternatives to address the limited availability of autografts and allografts [122]. Although grafted stents have yielded favorable outcomes to some degree, they fail to address key impediments in bone tissue restoration, including low bone induction rates, inadequate bone conductivity, and necrotic bone caused by insufficient vascularization [123]. SIS, which exhibits outstanding osteogenic and angiogenic activity, has significant potential to repair large bone defects.

Previous studies have shown that SIS membranes are beneficial in GBR therapy for new bone formation and maturation. Zihao Liu et al. assessed the GBR potential of SIS membrane. It has been found that SIS membranes not only have asymmetric structure and strong biocompatibility, but also promote the formation of calcium nodules and the expression of alkaline phosphatase (ALP), bone morphogenetic protein 2 (BMP-2), osteopontin (OPN) and runt-related transcription factor 2 (Runx2). After six weeks of implantation in a rat model with a skull defect, the SIS membrane group showed a significant increase in bone growth [124]. Moreover, An asymmetric SIS membrane was developed using liquid nitrogen quench and binding to the BMSC exosome through recombinantly engineered peptides (Fig. 3A). Additionally, mechanistic studies show that the PI3K/Akt signaling pathway plays a crucial role in exosome-induced osteogenic differentiation in BMSCs [117]. In addition, Jie Tan's report indicated that SIS hydrogels can induce macrophage polarization towards a combination of both M1 and M2 phenotypes, which can be augmented in vitro through the facilitation of angiogenesis-related cell migration and tube formation [118]. Additionally, there is a minor influence on angiogenesis and osteogenesis. Critically-sized bone defect regeneration experiments using rat models further demonstrate that the composite BMP-2@SIS hydrogels can activate M1 and M2 macrophages in sequence and establish early angiogenesis, leading to the accelerated regeneration of the final bone defect (Fig. 3B).

Various biocomposites prepared by SIS have been extensively explored for bone repair applications. William L. Chung et al. implanted the SIS stent in a model of the canine temporomandibular joint for medical removal and implantation. After 21 days, the histological tissue surrounding the device and draining lymph nodes displayed no adverse effects on the stent [125]. The SIS-derived ECM scaffold was utilized as a regenerative template for the TMJ disc in a pig model. Longitudinal MRI analysis revealed that the scaffold facilitated the development of new tissue in the joint space during the entire study period. After one month of implantation, the scaffold rapidly fills with host-derived cells and is reshaped by the formation of new, dense, neatly arranged fibrocartilage [126]. In another study, the decellularized extracellular matrix (ECM) of the submucosa from the small intestine of pigs is coated onto the surface of bioceramics (TBC) [127]. This is followed by mineralization modification (mSIS/TBC), after which an aspartate-modified bone morphogenetic protein 2 (BMP-2) peptide (P28) is immobilized to the scaffold without the use of crosslinkers. Results indicate that the P28/mSIS/TBC scaffold demonstrated significantly more osteogenic activity than both the TBC and mSIS/TBC groups based on alkaline phosphatase activity and other markers of osteogenic differentiation. Additionally, new bone areas and new blood vessel densities were evaluated in rat skull bone defect models with promising outcomes. Historical observations suggest that the P28/mSIS/TBC scaffold has a strong potential for bone regeneration.

4.3. Circulatory system

Cardiovascular disease remains a major global health challenge. The use of valves, meshes, and catheters is the basis for surgery to reconstruct the congenital heart, and synthetic grafts to replace damaged, occluded, and ruptured blood vessels have also been developed [128]. The optimal bioscaffold must fulfill crucial prerequisites: (i)biocompatibility, (ii)resilience to tissue calcification, thickening, and retraction, and (iii)limited ability to induce severe inflammation, fibrosis, or infection susceptibility [128,129]. Because the arrangement of collagen fibers in SIS membranes can provide significant strength and stiffness, and can meet the mechanical requirements of cardiovascular tissue engineering, it is often used for tissue repair of the cardiovascular system [130]. In addition, CorMatrix® has obtained licenses from both the U. S. Food and Drug Administration and the European CE mark among commercially available SIS-ECM products. It received approval for use in pericardial mesh repair and reconstruction, cardiac tissue repair,

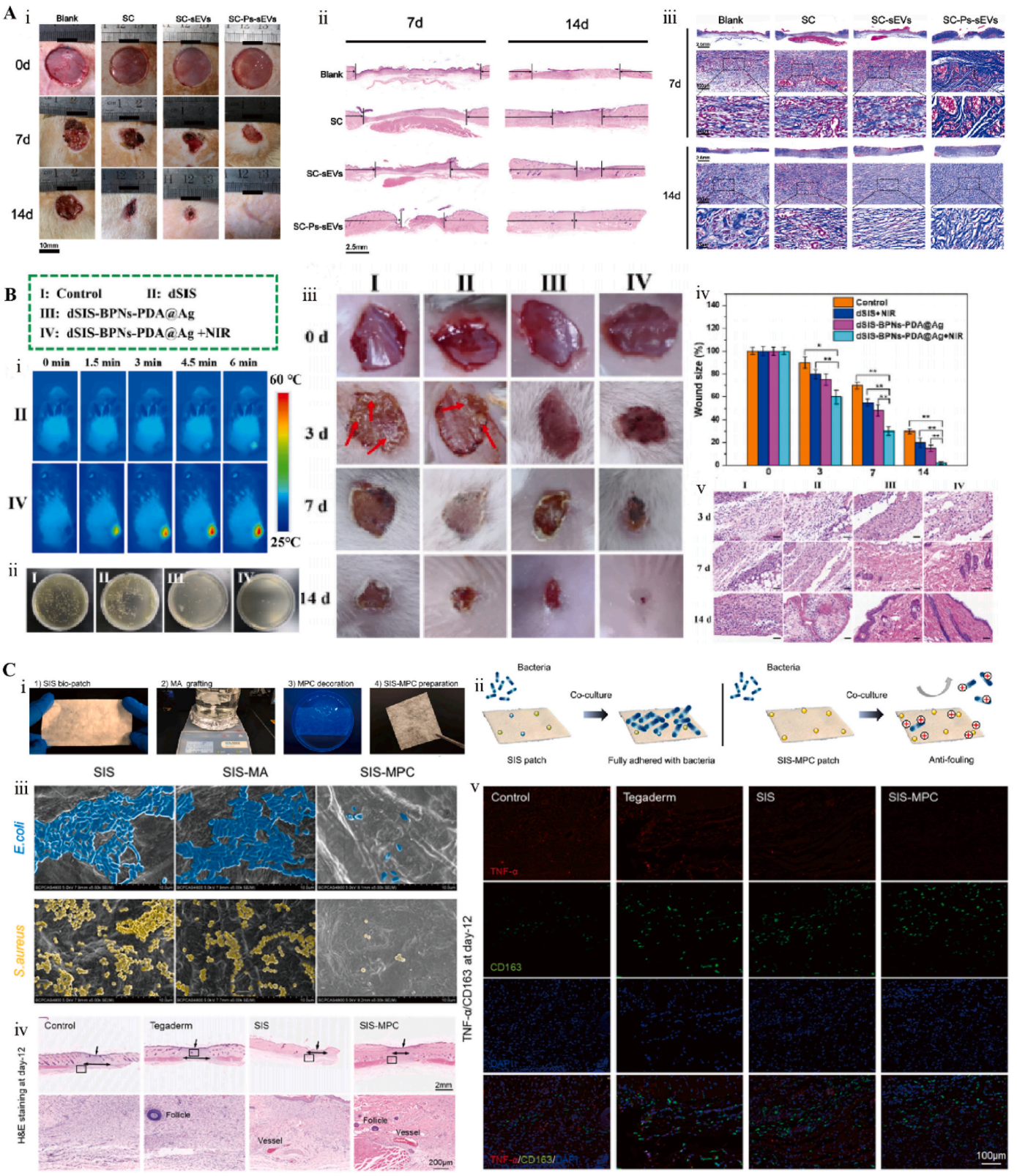

Fig. 2. Functional small intestinal submucosa in skin repair. (A) These findings demonstrate the ability of SC-Ps-sEVs hydrogel dressings to promote diabetic wound healing. Adapted reprinted with permission from Ref. [114] Based on CC BY License. (B) Application of dSIS-BPNs-PDA@Ag composite stents in infected wounds. Adapted reprinted with permission from Ref. [115] (License number:5,633,450,889,819). (C) SIS-MPC biopatches' function in the management of chronic wounds. Adapted reprinted with permission from Ref. [116] (License number:5,633,461,266,358).

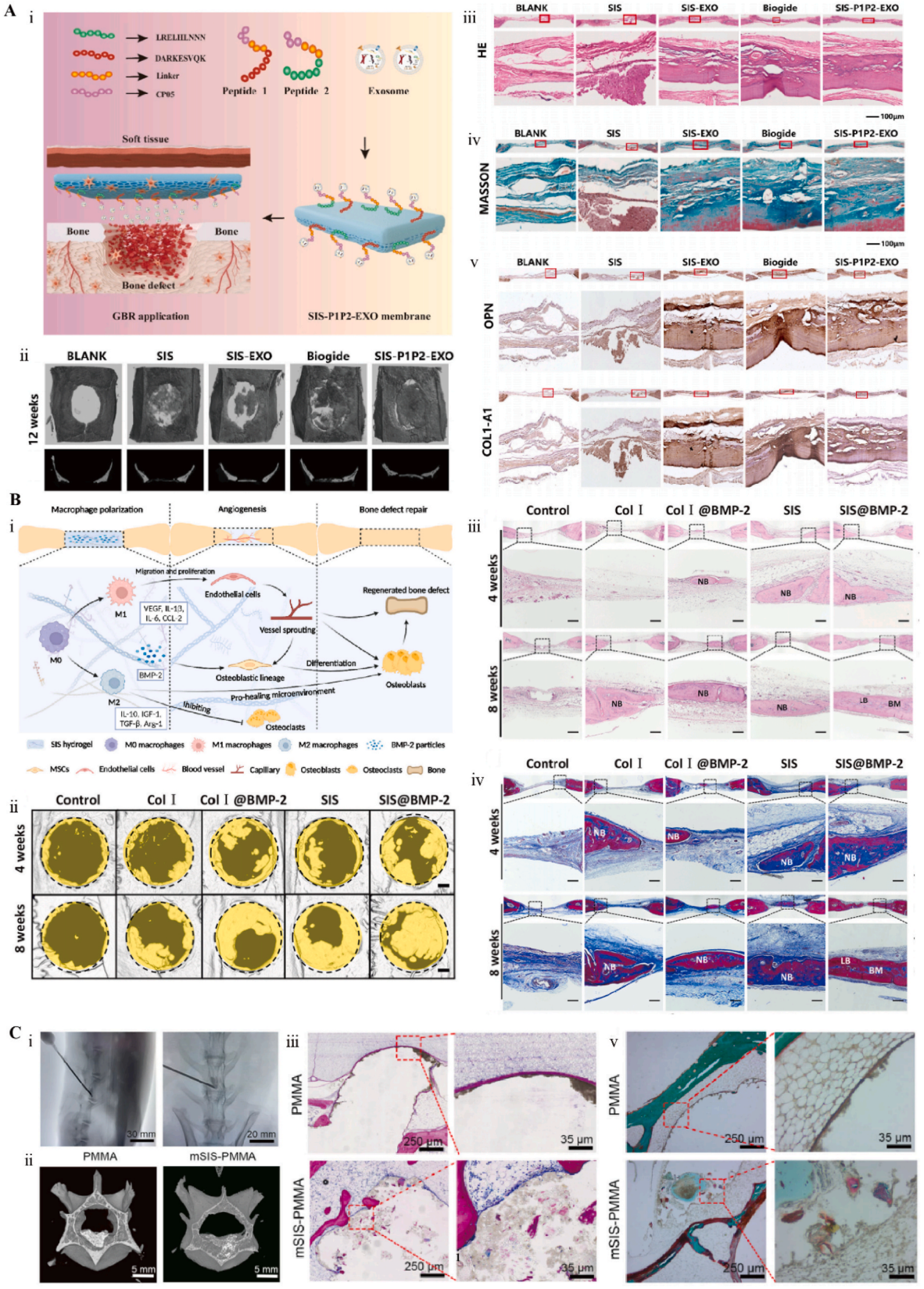

Fig. 3. Functional small intestinal submucosa in bone regeneration. (A) These findings demonstrate the ability of asymmetric SIS scaffolds to promote osteogenesis in vivo. Adapted reprinted with permission from Ref. [117](License number:5,633,471,337,898). (B) Application of composite BMP-2@SIS hydrogel in bone reconstruction. Adapted reprinted with permission from Ref. [118](License number:5,634,110,894,862). (C) Histological analysis of bone growth and regeneration of SIS-PMMA bone cement in a rabbit model of osteoporosis. Adapted reprinted with permission from Ref. [79] Based on CC BY License.

carotid artery repair, and encapsulated implantable electronics [131].

Research has demonstrated that injectable decellularized matrix hydrogel (pDSIS-gel) injected into the submucosa of the small intestine is effective for repairing myocardial injuries. pDSIS-gel aids in the growth, adhesion, spreading, and maintenance of normal pulsation of neonatal rat cardiomyocytes (NRCMs) (Fig. 4B) [132]. Brittany A. Gonzalez et al. assessed the immediate function and potential for somatic growth of the 2-layer PSIS mitral valve structure that was implanted in juvenile baboons (n = 3). The valve exhibited robust functionality in all animals. Subsequent experiments demonstrated the capability of the PSIS mitral valve to regenerate ECM components such as proteoglycans, elastin, and collagen in the primary valve tissue [91]. Additionally, PSIS mitral valves demonstrated cellular regularization of valve phenotype, marked by smooth muscle cell (α-SMA) and endothelial cell (CD31) positivity. CD31-positive staining gradually transitioned to the surface of PSIS valves over longer implantation periods, and 20-month-old PSIS valve grafts had comparable CD31-positive staining surface distribution to native baboon mitral valve leaflets (Fig. 4A) [133]. Su-Ya Wang's study sheds light on the mechanism behind SIS gel's effectiveness in treating myocardial infarction. The gel secures cardiomyocytes from apoptosis by inhibiting pro-inflammatory cytokine expression (TNF-α, CCL2, and IL-6) and preventing downregulation of the JNK-MAPK/NF-KB pathway. Additionally, the gel significantly upregulates the expression of anti-apoptotic Bcl-2 while inhibiting the expression of pro-apoptotic Bax and c-caspase 3. Additionally, small-diameter vascular grafts that are cell-free, based on functionalizing small intestinal submucosa with heparin and VEGF, were successfully manufactured and implanted into the arterial system of neonatal lambs [82]. These grafts remained patent and grew in size with the host to a similar extent and rate as native arteries. Qin Fang reported a hybrid artificial vascular graft with a small diameter which is based on bilayer SIS. The graft uses a gel polysaccharide and dipyridamole mixture membrane as a sandwich filler. Results demonstrate that during carotid artery bypass implantation in rabbits, the graft remained fully open after 2 months, improving the patency of the implantation in the new small-bore artificial vascular graft [134]. To showcase the crucial role of SIS in developing coronary artery bypass graft substitutes, Pan Zhao et al. discussed building tissue-engineered biologically active small blood vessels. The process involved using secretory Klotho (SKL) and heparin crosslinked with SIS, with SKL enhancing endothelial cell growth and adhesion. This led to better platelet adhesion and hence improved small vessel permeability. After three months of being implanted in a rabbit carotid bypass model, the SKL-modified vascular grafts retained patency, decreased thrombosis formation, and facilitated

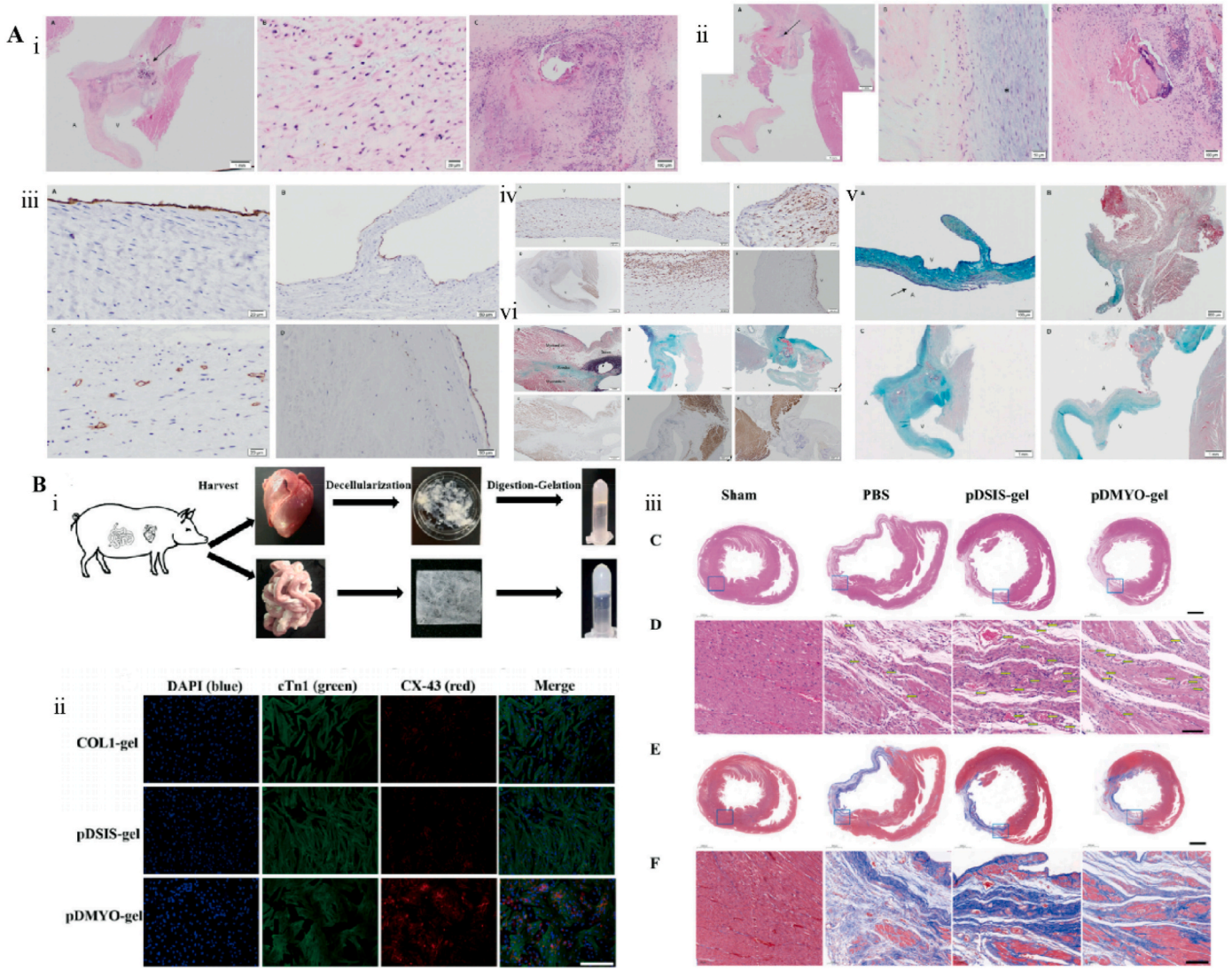

Fig. 4. Functional small intestinal submucosa in cardiac repair. (A)Application of SIS biological scaffolds in juvenile non-human primate models for mitral valve replacement. Adapted reprinted with permission from Ref. [133] Based on CC BY License. (B)Effect of decellularized matrix hydrogels on acute myocardial infarction in rats. Adapted reprinted with permission from Ref. [132] Based on CC BY License.

epithelialization [108].

4.4. Urinary system

Dysfunction of the urinary system or complex injury to the urinary tract necessitates surgical reconstruction to decrease incontinence, maintain bladder storage function, and lessen the risk of kidney damage [135]. Biomaterial scaffolds have emerged in tissue engineering as a biomimetic alternative for reconstructing the complex structure and function of natural urinary systems. Several acellular matrices and natural and synthetic polymer scaffolds have been developed. SIS has seen gradual utilization in urinary tract reconstruction over recent years.

Biomaterials and scaffolds ought to possess structures that have suitable mechanical properties, withstand physiological contraction and expansion pressures, and facilitate cell migration [136]. In one study, the natural bio-crosslinking agent proanthocyanidin (PC) and SIS were cross-linked by hydrogen bonding to improve the mechanical properties and stability of SIS. The PC-SIS patch yielded better bladder function than the SIS patch alone in a rabbit model of full-thickness bladder defect by promoting smooth muscle regeneration, improving bladder compliance, and avoiding progressive kidney disease (Fig. 5A) [98]. In another one, Yu-Ting Song has developed an efficient and specific stem cell trapping scaffold. The results of in vivo experiments indicate that AC-SIS, which are SIS scaffolds conjugated with anti-CD29 antibodies, promote rapid healing of endothelial tissue and regeneration of smooth muscle (Fig. 5B) [137]. Additionally, bone-marrow (BM) mesenchymal stem cells (MSCs) were co-seeded with $CD34^{+}$ hematopoietic stem/-progenitor cells (HSPCs) in SIS scaffolds to investigate their contribution to bladder tissue regeneration, and the results showed that increasing cell seeding density had the potential to enhance bladder tissue regeneration in the model [106]. Liao Peng and colleagues developed a cellular remodeling analysis and discovered vital cell subsets and genes that prompt bladder remodeling. The remodeled analysis contains thirteen cell types, with fibroblasts, smooth muscle cells, endothelial

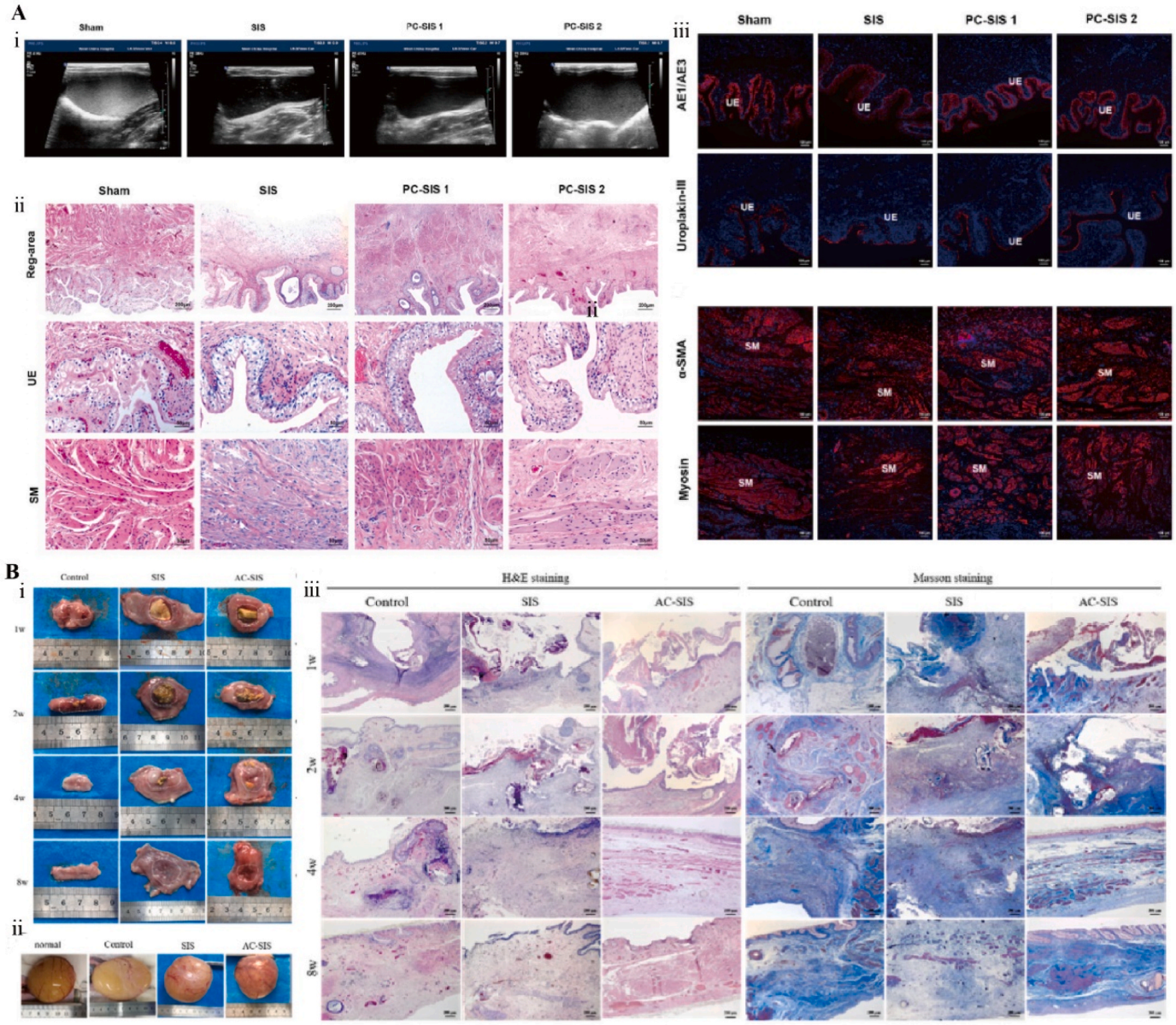

Fig. 5. Functional small intestinal submucosa in urinary system repair. (A) Application of proanthocyanidin crosslinking the submucosa of the small intestine in bladder repair. Adapted reprinted with permission from Ref. [98]. (B) Macroscopic observation and histological examination of the regenerated bladder. Adapted reprinted with permission from Ref. [137].

cells, and macrophages communicating most frequently with other cells. Of these cells, Saa3 fibroblasts may play a role in mediating tissue remodeling [138]. Furthermore, Shivang Sharma et al. achieved successful bladder regeneration utilizing SIS which had been modified by long aliphatic chains (C9, C14, and C18). This modification increased the SIS's resistance to enzymes and subsequently reduced the incidence of stone formation by 50% in a rat bladder enlargement model [139]. Li-Ping Huang et al. described the production of multifunctional patches composed of PCA/SIS for mending urinary tract defects. The method involved blending protocatechinaldehyde (PCA) with the SIS of the small intestine in alkaline conditions to allow for cross-linking and to confer antioxidant and anti-inflammatory properties to SIS [97]. *In vitro* studies demonstrate that the patch greatly enhances adhesion, orientational extension, and proliferation of R-EMC and R-SMCs. Additionally, it upregulates the expression of keratin and SMC contractile proteins in EMC. This evidence supports the efficacy of the patch in promoting cellular growth and protein expression. More importantly, in vivo studies have demonstrated that PCA/SIS patches can markedly enhance scar-free healing of urethral defects in rabbits by stimulating regeneration of smooth muscle, reducing excessive collagen deposition, and accelerating reepithelialization and neovascularization.

4.5. Reproductive system

Severe uterine injury resulting from curettage, infection, miscarriage, or damage to the basal, epithelial, and vascular layers of the endometrium has limited natural reparative capacity [140]. With the advancements in tissue engineering, it is now feasible to repair uterine damage. SIS presents novel prospects for endometrial repair due to its capacity to remodel the normal tissue structure and function by epithelialization and vascularization.

For example, Mingyue Qu et al. reported on the effects of the combination of SIS tissue engineering materials with umbilical cord mesenchymal stem cells (UC-MSCs) on uterine injury in female rats after holography [103]. The results indicated that granulation tissue and inflammatory cell infiltration were visible in all groups 1–2 weeks post-surgery, and fibroblasts secreted collagen fibers. By the fourth week, the uterine cavity at the resection site was fully covered with epithelium, inflammatory cell infiltration was normal, and collagen fibers were abundant. Glands, stromal cells, and smooth muscle cells had also been repaired. Smooth muscle in the SIS group was higher than in the control group. The transverse medial muscles of the group treated with UC-MSCs-SIS remain intact and exhibit greater continuity compared to the other two groups. At the eight-week marker post-surgery, the UC-MSCs-SIS group revealed a profusion of surface capillaries, whereas both the SIS and control groups displayed paler surface colors indicative of inadequate blood supply. After eight weeks of natural healing, the proportion of the uterus in the repair zone that supported the growth of live embryos, the pregnancy rate, the number of viable embryos, and their proportion, were significantly lower than in the UC-MSCs-SIS group. Additionally, YuTing Song et al. utilized SIS cross-linking with genipin (GP-SIS) to reload urine-derived stem cells (USC) for the regeneration of the endometrium (Fig. 6A) [100]. GP-SIS stents have excellent biocompatibility and good mechanical properties. *In vitro*, they facilitate the migration of epithelial cells and promote angiogenesis. When transplanted into rats with IUA attributed to endometriosis, GP-SIS/USCs transplantation was found to preserve normal luminal structure, stimulate regeneration of the endometrium and glands, impede the formation of fibrous tissue, induce vascularization, and enhance endometrial receptivity Furthermore, SIS has been utilized for vaginal reconstruction. Full-thickness defects were created in the vaginal walls of ten mini-pig donors. Four centimeters of the vaginal walls were removed and replaced with SIS scaffolds of the same size. After four weeks, reorganization occurred in the extracellular matrix and the vaginal epithelium started covering the lumen stromal surface, along with the formation of microvascular networks and the regeneration of smooth muscle. After 12 weeks, improvements were observed in the formation of multilayer squamous epithelium, angiogenesis, and the formation of large muscle bundles in the vagina. These findings suggest the involvement of the Hippo signaling pathway in the angiogenesis of the new vagina [141].

4.6. Functional SIS in other systems

4.6.1. Muscular system

Injuries to muscles and tendons, including ligaments, are common. One significant impediment to repairing muscle and tendon injuries is the development of restrictive adhesions. SIS has demonstrated potential benefits by enhancing the histological appearance and promoting better tissue and cross-sectional growth of tendons, thereby facilitating the guidance of muscle and tendon formation. For instance, Xing Guo conducted research on the application of SIS in mending ruptured Achilles tendons, indicating the potential benefits of SIS in tendon engineering [142]. In the rat Achilles tendon defect model, SIS scaffolds seeded with adipose-derived mesenchymal stem cells (ADSCs) showed increased expression of tendon-related genes with hypoxic preconditioning. Additionally, after transplantation of Achilles tendon defects, there was an increase in fracture load. Additionally, the

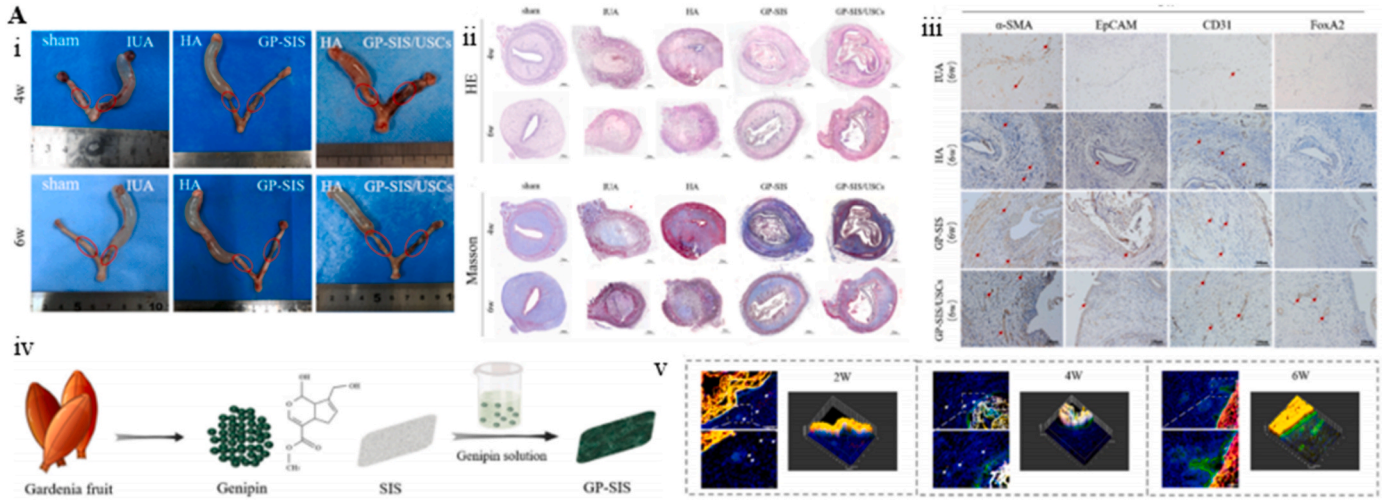

Fig. 6. Functional small intestinal submucosa in reproductive system repair. (A) In vivo study of the endometrial regeneration by the GP-SIS/USCs in the rat model for IUA. Adapted reprinted with permission from Ref. [100] (License number:5,633,540,098,063).

incorporation of tendon-derived stem cells (TDSCs) onto SIS scaffolds to create TDSC-SIS scaffolds facilitates the regeneration of the Achilles tendon and prevents adhesions through M2 polarization of macrophages. SIS scaffolds fostered cell attachment and tendon specialization of TDSCs, and the expression of TGF-β and ARG-1 in the TDSCs-SIS scaffold group on days 3 and 7 surpassed that of the TDSCs group [143]. *In vivo*, the implanted TDSCs-SIS scaffold significantly improved tendon regeneration and decreased adhesion. The TDSCs-SIS stent group showed significantly higher expression of CD163 and significantly lower expression of CD68 compared to the other two groups. Additionally, Xuancheng Zhang developed a novel, enhanced, low-immunogenic submucosal (SIS) mesh of the small intestine to repair supraspinatus tendon defects in rabbit models [144]. A model of supraspinatus tendon deficiencies was generated in thirty-six rabbits (seventy-two shoulders). Both shoulders were picked at random for mending via SIS mesh (SIS group) or autologous fascia lata (FL group). The use of an improved, hypo-immunosuppressive SIS mesh for restoring large supraspinatus tendon deficiencies has displayed comparable outcomes to autologous FL in rabbit models. This innovative mesh might prove valuable as a structural tissue substitute in medical procedures.

4.6.2. Respiratory system

Several studies have evaluated SIS as a potential treatment for trachea repair. It is worth noting, however, that further research is needed to fully explore the benefits and limitations of SIS for trachea repair. Cinthia Galvez Alegria researched the use of SIS versus acellular bilayer silk fibroin (BLSF) grafts for repairing full-thickness tracheal defects in a durable rat model. The BLSF and SIS scaffolds helped with initial defect consolidation, with survival rates of 94% and 100%, respectively, three months after tracheal integration. Animals that received BLSF or SIS biomaterials did not display any respiratory distress symptoms and were able to maintain a patent and unobstructed endotracheal tube, according to a necropsy assessment. SIS grafts encouraged the regeneration of airway mucosa at the implant site, and the majority of SIS implants degraded within a month of surgery [145]. A recent survey reported that SIS mesh treated with a vacuum system exhibited superior cell attachment and viability compared to the control group [146]. Moreover, the in vivo findings indicated that the repair of tracheal defects using degassed SIS mesh demonstrated improved healing, fibrosis, and luminal stenosis in contrast to the control group employing ungassed SIS. Furthermore, the degassed SIS mesh group revealed a notable reduction in graft thickness compared to the control group. The degassing of SIS mesh effectively mitigates luminal fibrosis and stenosis, and simultaneously, significantly promotes cellular patch adhesion and wound healing. Additionally, a study revealed that the transplantation of the submucosal extracellular matrix (SIS-ECM) derived from the small intestine with gingival mesenchymal stem cells (GMSC) or their exosomes considerably augmented papilla reactivation and taste bud repair [105]. This was corroborated by increased expression of CK14, CK8, and type I, II, and III taste bud cell markers (NTPdase 2, PLC-β2, and AADC, correspondingly). The animals treated with GMSC/SIS-ECM or exosomes/SIS-ECM displayed elevated levels of Sonic Hedgehog (Shh) expression in the injured area of the tongue. Shh plays a crucial role in the development, homeostasis, and retention of taste bud organs. Moreover, GMSC or its exosomes reinforce the regenerative innervation of taste buds, as demonstrated by the augmented nerve filaments and P2X3 expression in the damaged region.

4.6.3. Abdomen

Abnormalities in the abdominal wall present a significant challenge in the field of regenerative medicine. Throughout the years, a variety of natural and man-made mesh materials have been developed to address these defects. However, these materials have their limitations. They are unable to degrade naturally and are not capable of promoting tissue regeneration. Consequently, these shortcomings can lead to the development of severe abdominal adhesions and chronic discomfort in patients. To overcome these limitations, researchers have turned to the extracellular matrix (ECM) as a potential solution. One particular example of ECM is small intestine submucosa (SIS). This material not only possesses degradable properties but also exhibits the capacity to regenerate tissues. The ECM contains a complex architecture designed by nature, along with various growth factors that facilitate the constructive remodeling and functional restoration of tissues. In one study conducted by Guangxiu Cao, fluorescent dye Cy5.5 NHS ester in the near-infrared (NIR) range was used to label ECM-based composites composed of SIS and chitosan/elastin electrospun nanofibers. These composites were then monitored in real-time and noninvasively. This approach allowed for the accurate determination of the biodistribution and clearance of the degraded product until complete degradation was achieved [147]. In a model involving full-thickness abdominal defects, the composite showed no signs of over-inflated or fibrotic capsules, which could potentially positively affect the polarization of M2-like macrophages. Furthermore, the fusion peptide, composed of a collagen-binding peptide and CP05, modified the SIS membrane through the infusion of extracellular vesicles derived from mesenchymal stem cells. *In vitro* studies demonstrated that modified SIS membranes enhanced cell migration and proliferation, likely due to the activation of TEADs, which regulate cell behavior. The modified SIS exhibited improved biocompatibility, a reduction in inflammatory cells, earlier cardiovascular formation, and an increase in collagen deposition in a rat model with abdominal wall defects [148].

4.6.4. Nervous system

The nervous system encompasses two distinct components, namely the peripheral nervous system and the central nervous system. The latter is composed of the spinal cord and brain. These work in tandem to produce and transmit signals. These components work together to create and transmit signals. Autologous nerve transplantation is associated with a limited supply of nerves from donors, the need for additional surgical sites, the possibility of complications at the surgical sites, and the potential for size differences. Rasa Zhukauskas et al. conducted a study on the host's subchronic response to implants using the Axoguard neural connector, made from SIS, and the NeuraGen neural catheter, made from cross-linked bovine type I collagen (Col), in a rat model of sciatic nerve defect. The results of the study showed that the SIS group exhibited a predominance of macrophage type 2 (M2) response, whereas the Col group showed a predominance of macrophage type 1 (M1) response [149]. The SIS group also had higher levels of implant vascularization and fibroblast growth compared to the Col group. Moreover, collagen deposition in lumens was greater in the Col group than in the SIS group.

5. Clinical applications of SIS

As highlighted earlier, the effective employment of SIS biological scaffolds across multiple research domains has laid the groundwork for its application in clinical therapies. To date, SIS has achieved considerable progress in treating conditions such as abdominal hernias, full-thickness skin defects, bladder and vaginal defects, and eardrum repairs [150–154]. These clinical applications have yielded impressive results. For instance, a systematic review and meta-analysis examining different biomeshes in ventral hernia repair found no significant differences in recurrence rates and surgical site infections at a 1-year follow-up among porcine small intestinal submucosal grafts, non-cross-linked human acellular dermal matrix (NCHADM), non-cross-linked porcine ADM (NCPADM), non-cross-linked bovine ADM (NCBADM), and cross-linked porcine ADM (CPADM) [155]. In abdominal hernia repair surgeries, SIS has proven to provide durable support and strength, effectively repairing and reinforcing the area within the hernia sac. Additionally, a retrospective study on vaginoplasty found no significant discrepancies in the Female Sexual Function Index (FSFI) total scores or male partner satisfaction between

groups using SIS grafts and those undergoing Sheares vaginoplasty or laparoscopic surgery [156]. SIS offers enduring structural support and vertical tension, successfully addressing vaginal defects in patients. Furthermore, a study by Florence Cour et al. on the use of small intestinal submucosal xenografts for treating lower urinary tract prosthesis perforation reported the safety and efficiency of absorbable SIS grafts in addressing urethral tape and mesh perforations within the lower urinary tract [157].

The primary commercially available SIS grafts include CuffPatch™, Oasis wound matrix, Surgisis™, CorMatrix™, and Biodesign™ [158–163]. CuffPatch™, comprising 97% collagen and 2% elastin, is 8 layers thick and measures 6.5 × 9 cm [164]. Although often used as a tendon substitute graft, in vitro experiments indicated CuffPatch™ lacks the necessary tensile strength [165] , and clinical trials for tendon repair utilizing CuffPatch™ are currently unavailable. The Oasis wound matrix, renowned for its unique biological properties since 1989, has been extensively used in wound healing [166]. A 2005 randomized controlled trial for diabetic foot ulcers over 12 weeks showed that Oasis wound matrix treatment was as effective as Regranex gel in healing full-thickness diabetic foot ulcers within the timeframe [167]. Additionally, Oasis wound matrix has been used as an adjunct therapy, significantly enhancing the healing of chronic leg ulcers [168]. Recently, a study by Marie Brown-Etris et al. assessed the Oasis wound matrix in treating full-thickness pressure ulcers, finding that its use resulted in a 90% reduction in wound size compared to standard care alone [169]. Surgisis™ is another SIS biological matrix available commercially. In a clinical trial with 123 patients experiencing capsular defects after partial nephrectomy, only 4 reported urinary leakage, supporting the use of Surgisis™ in preventing complications like postoperative bleeding and urinary fistula in nephron-sparing surgeries [170]. Vasileios Alexandridis et al.'s review on Surgisis™ effectiveness in pelvic organ prolapse repair revealed that 56% of women encountered complications, mainly urinary retention (19%) and pain (12%), within three months post-surgery [171]. CorMatrix™, a prevalent SIS-ECM stent in the cardiovascular field, has been suggested by a systematic review to possess many "ideal" scaffold characteristics. The available clinical data, though not exhaustive, indicate minimal excessive calcification, thickening, or retraction, showcasing its successful use in pediatric populations [128]. Biodesign™, another acellular intestinal submucosal matrix option, has demonstrated safety and effectiveness as a mesh for hernia repair in a multicenter, double-blind randomized controlled trial, with no patients experiencing hernia relapse at a six-month follow-up [172].

Despite the extensive application of SIS in clinical trials, several limitations persist. Firstly, current studies are predominantly retrospective and lack the rigorous sample size necessary for conclusive randomized controlled studies. Thus, future studies should be meticulously designed, with proper sample sizes calculated and the conduct of multicenter studies strengthened. Secondly, while the benefits of SIS have been substantiated by clinical data, attention must be given to its potential infectious and inflammatory responses as a xenograft. Additionally, standardizing the commercial processes and reducing production costs of SIS are crucial to enhancing its economic and social value. Finally, the exact mechanisms through which SIS promotes wound healing remain unclear, warranting further comprehensive research and exploration.

6. Conclusion and perspectives

SIS has garnered significant interest in the tissue repair domain attributed to its remarkable biocompatibility and biological activity, efficient absorption, weak immunogenicity, and potent aptitude to foster natural tissue growth. During production, SIS can undergo surface modification in numerous ways to fine-tune its mechanical and biological characteristics. Numerous studies indicate that SIS is a highly versatile tissue biomaterial that holds great potential in overcoming the challenges of repairing both soft and hard tissue. SIS has been applied successfully in tissue engineering for various organs, including the myocardium, bladder, skin, cartilage, and others. Hence, SIS represents a promising avenue for tissue regeneration.

Despite the significant progress made by SIS in tissue engineering, ongoing challenges persist in meeting the demanding clinical applications of the future.

First, there is a need for standardized decellularization protocols and characterization methods, in addition to standardized manufacturing processes and functional quality control of products, to more effectively preserve the biological and mechanical properties of SIS, while also conducting more sensitive testing of residual cellular components and toxic products. In addition, it is worth noting that SIS comprises diverse bioactive molecules whose involvement in tissue regeneration has yet to be extensively researched. The intrinsic mechanisms of bioactive molecules, signaling pathways specifically, remain to be fully elucidated. The intrinsic mechanisms of bioactive molecules, signaling pathways specifically, remain to be fully elucidated. Further research is necessary to shed more light on these topics.

Secondly, it is imperative to further enhance the SIS functionalization method by incorporating cross-links of loading factors, biologically active molecules, and/or scaffolds to facilitate tissue repair and regeneration. The regularization process should thoroughly consider clinically relevant renewable cell sources and inoculation methods. While using SISECM and stem cells together as a tissue graft has demonstrated enhanced regenerative outcomes for various tissue defects, the mechanisms behind the interaction between the stem cell-SISECM scaffold are still unknown. Further research to clarify the biological functions and capabilities of SIS-ECM in facilitating efficient stem cell delivery may lead to new potential applications for tissue repair. Additionally, it is necessary to investigate the role of macrophages in stem cell tissue regeneration/SIS-ECM and to give further attention to the crosstalk between macrophages and stem cells for studying the foreign body response. Exciting possibilities exist in developing new strategies to specifically regulate macrophages and stem cells in SIS-based materials for tissue regeneration.

Finally, concerns exist that the immune properties may be reduced due to the complete decellularization of SIS. Patients treated with heterologous SIS often experience psychological rejection and anxiety regarding the potential harms of SIS. Additionally, using animal-derived sources in humans poses a risk that may negatively impact tissue repair and require additional attention. Immunogenicity and biocompatibility evaluations are crucial for obtaining final authorization from health agencies, securing commercial feasibility, and facilitating clinical implementation.

Ethical statement

There are no animal experiments carried out in this article.

CRediT authorship contribution statement

Yifan Zhao: Conceptualization. **Hongyi Peng:** Writing – review & editing, Writing – original draft, Visualization. **Lingxiang Sun:** Data curation. **Jiahui Tong:** Writing – review & editing. **Chenying Cui:** Data curation. **Ziyang Bai:** Data curation. **Jingyu Yan:** Supervision. **Danlei Qin:** Supervision. **Yingyu Liu:** Data curation. **Jue Wang:** Funding acquisition. **Xiuping Wu:** Project administration. **Bing Li:** Project administration.

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

No data was used for the research described in the article.

Acknowledgments

This work is supported by the Science and Technology Innovation Leader and Key Talent Team Project of Shanxi Province (202204051002034), National Natural Science Foundation of China (82003146), Key Research and Development Plan of Shanxi Province (202102130501002), Scientific Research Project for Returned Overseas Professionals of Shanxi Province (2022-120), Key national science and technology cooperation project of Shanxi Provincial Department of Science and Technology (202204041101004) and Four "Batches" Innovation Project of Invigorating Medical through Science and Technology of Shanxi Province (2023XM013).

References

[1] I. Matai, G. Kaur, A. Seyedsalehi, A. McClinton, C.T. Laurencin, Progress in 3D bioprinting technology for tissue/organ regenerative engineering, Biomaterials 226 (2020) 119536, https://doi.org/10.1016/j.biomaterials.2019.119536.

[2] P. Wu, H. Chen, R. Jin, T. Weng, J.K. Ho, C. You, L. Zhang, X. Wang, C. Han, Non-viral gene delivery systems for tissue repair and regeneration, J. Transl. Med. 16 (2018) 29, https://doi.org/10.1186/s12967-018-1402-1.

[3] M.S. Carvalho, A.A. Poundarik, J.M.S. Cabral, C.L. da Silva, D. Vashishth, Biomimetic matrices for rapidly forming mineralized bone tissue based on stem cell-mediated osteogenesis, Sci. Rep. 8 (2018) 14388, https://doi.org/10.1038/s41598-018-32794-4.

[4] A.A. Ivanov, A.V. Kuznetsova, O.P. Popova, T.I. Danilova, O.O. Yanushevich, Modern approaches to acellular therapy in bone and dental regeneration, Int. J. Mol. Sci. 22 (2021) 13454, https://doi.org/10.3390/ijms222413454.

[5] R. Langer, J. Vacanti, Advances in tissue engineering, J. Pediatr. Surg. 51 (2016) 8–12, https://doi.org/10.1016/j.jpedsurg.2015.10.022.

[6] F.J. O'Brien, Biomaterials & scaffolds for tissue engineering, Mater. Today 14 (2011) 88–95, https://doi.org/10.1016/s1369-7021(11)70058-x.

[7] W.L. Murphy, T.C. McDevitt, A.J. Engler, Materials as stem cell regulators, Nat. Mater. 13 (2014) 547–557, https://doi.org/10.1038/nmat3937.

[8] P.J. Yang, M.E. Levenston, J.S. Temenoff, Modulation of mesenchymal stem cell shape in enzyme-sensitive hydrogels is decoupled from upregulation of fibroblast markers under cyclic tension, Tissue Eng. 18 (2012) 2365–2375, https://doi.org/10.1089/ten.tea.2011.0727.

[9] S. Khetan, M. Guvendiren, W.R. Legant, D.M. Cohen, C.S. Chen, J.A. Burdick, Degradation-mediated cellular traction directs stem cell fate in covalently crosslinked three-dimensional hydrogels, Nat. Mater. 12 (2013) 458–465, https://doi.org/10.1038/nmat3586.

[10] M. Wang, Developing bioactive composite materials for tissue replacement, Biomaterials 24 (2003) 2133–2151, https://doi.org/10.1016/s0142-9612(03)00037-1.

[11] A.S. Rowlands, S.A. Lim, D. Martin, J.J. Cooper-White, Polyurethane/poly(lactic-co-glycolic) acid composite scaffolds fabricated by thermally induced phase separation, Biomaterials 28 (2007) 2109–2121, https://doi.org/10.1016/j.biomaterials.2006.12.032.

[12] K.M. Naegeli, M.H. Kural, Y. Li, J. Wang, E.A. Hugentobler, L.E. Niklason, Bioengineering human tissues and the future of vascular replacement, Circ. Res. 131 (2022) 109–126, https://doi.org/10.1161/CIRCRESAHA.121.319984.

[13] L. Guo, Z. Liang, L. Yang, W. Du, T. Yu, H. Tang, C. Li, H. Qiu, The role of natural polymers in bone tissue engineering, J. Contr. Release 338 (2021) 571–582, https://doi.org/10.1016/j.jconrel.2021.08.055.

[14] L.T. Saldin, M.C. Cramer, S.S. Velankar, L.J. White, S.F. Badylak, Extracellular matrix hydrogels from decellularized tissues: structure and function, Acta Biomater. 49 (2017) 1–15, https://doi.org/10.1016/j.actbio.2016.11.068.

[15] L. Cui, Y. Zhao, Y. Zhong, L. Zhang, X. Zhang, Z. Guo, F. Wang, X. Chen, H. Tong, J. Fan, Combining decellularized adipose tissue with decellularized adventitia extravascular matrix or small intestinal submucosa matrix for the construction of vascularized tissue-engineered adipose, Acta Biomater. (2023), https://doi.org/10.1016/j.actbio.2023.08.060. S1742-7061(23)00525–1.

[16] M.C. Prewitz, F.P. Seib, M. von Bonin, J. Friedrichs, A. Stißel, C. Niehage, K. Müller, K. Anastassiadis, C. Waskow, B. Hoflack, M. Bornhäuser, C. Werner, Tightly anchored tissue-mimetic matrices as instructive stem cell microenvironments, Nat. Methods 10 (2013) 788–794, https://doi.org/10.1038/nmeth.2523.

[17] G. Cao, Y. Huang, K. Li, Y. Fan, H. Xie, X. Li, Small intestinal submucosa: superiority, limitations and solutions, and its potential to address bottlenecks in tissue repair, J. Mater. Chem. B 7 (2019) 5038–5055, https://doi.org/10.1039/c9tb00530g.

[18] T. Matsumoto, R.H. Holmes, C.O. Burdick, 3rd C A Heisterkamp, J. T J O'Connell, Replacement of large veins with free inverted segments of small bowel: autografts of submucosal membrane in dogs and clinical use, Ann. Surg. 164 (1966) 845, https://doi.org/10.1097/00000658-196611000-00009.

[19] G.E. Sandusky, S.F. Badylak, R.J. Morff, W.D. Johnson, G. Lantz, Histologic findings after in vivo placement of small intestine submucosal vascular grafts and saphenous vein grafts in the carotid artery in dogs, Am. J. Pathol. 140 (1992) 317–324. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1886438/. (Accessed 22 September 2023).

[20] C.D. Prevel, B.L. Eppley, D.J. Summerlin, R. Sidner, J.R. Jackson, M. McCarty, S. F. Badylak, Small intestinal submucosa: utilization as a wound dressing in full-thickness rodent wounds, Ann. Plast. Surg. 35 (1995) 381–388.

[21] P.M. Knapp, J.E. Lingeman, Y.I. Siegel, S.F. Badylak, R.J. Demeter, Biocompatibility of small-intestinal submucosa in urinary tract as augmentation cystoplasty graft and injectable suspension, J. Endourol. 8 (1994) 125–130, https://doi.org/10.1089/end.1994.8.125.

[22] S.F. Badylak, R. Tullius, K. Kokini, K.D. Shelbourne, T. Klootwyk, S.L. Voytik, M. R. Kraine, C. Simmons, The use of xenogeneic small intestinal submucosa as a biomaterial for Achilles tendon repair in a dog model, J. Biomed. Mater. Res. 29 (1995) 977–985, https://doi.org/10.1002/jbm.820290809.

[23] C.D. Prevel, B.L. Eppley, D.J. Summerlin, J.R. Jackson, M. McCarty, S.F. Badylak, Small intestinal submucosa: utilization for repair of rodent abdominal wall defects, Ann. Plast. Surg. 35 (1995) 374–380.

[24] S. Jelodari, E. Sadroddiny, Decellularization of small intestinal submucosa, Adv. Exp. Med. Biol. 1345 (2021) 71–84, https://doi.org/10.1007/978-3-030-82735-9_7.

[25] L. Yang, J. Zhou, K. Yu, S. Yang, T. Sun, Y. Ji, Z. Xiong, X. Guo, Surface modified small intestinal submucosa membrane manipulates sequential immunomodulation coupled with enhanced angio- and osteogenesis towards ameliorative guided bone regeneration, Mater. Sci. Eng., C 119 (2021) 111641, https://doi.org/10.1016/j.msec.2020.111641.

[26] Z.-Y. Xu, L.-X. Li, X.-G. Wang, M.-X. Wang, G.-J. Cao, B.-L. Chen, S.-J. Liu, The long-term outcomes of vaginoplasty using acellular porcine small intestinal submucosa grafts in patients with Mayer-Rokitansky-Küster-Hauser syndrome: a case series, BJOG 130 (2023) 645–652, https://doi.org/10.1111/1471-0528.17388.

[27] M.J. Tjørnild, L. Carlson Hanse, S.N. Skov, K.B. Poulsen, M. Sharghbin, L. L. Benhassen, F. Waziri, D.M. Røpcke, S.L. Nielsen, J.M. Hasenkam, Entire mitral reconstruction with porcine extracellular matrix in an acute porcine model, J. Thorac. Cardiovasc. Surg. 160 (2020) 102–112, https://doi.org/10.1016/j.jtcvs.2019.07.085.

[28] I. Ghanad, M.D. Polanik, D.R. Trakimas, R.M. Knoll, M. Castillo-Bustamante, N. L. Black, E.D. Kozin, A.K. Remenschneider, A systematic review of nonautologous graft materials used in human tympanoplasty, Laryngoscope 131 (2021) 392–400, https://doi.org/10.1002/lary.28914.

[29] J.A. Gastel, W.R. Muirhead, J.T. Lifrak, P.D. Fadale, M.J. Hulstyn, D.P. Labrador, Meniscal tissue regeneration using a collagenous biomaterial derived from porcine small intestine submucosa, Arthroscopy 17 (2001) 151–159, https://doi.org/10.1053/jars.2001.20959.

[30] M.J. Pitman, T. Kurita, M.E. Powell, E.E. Kimball, M. Mizuta, S. Chang, C. G. Garrett, B. Rousseau, Vibratory function and healing outcomes after small intestinal submucosa biomaterial implantation for chronic vocal fold scar, Laryngoscope 128 (2018) 901–908, https://doi.org/10.1002/lary.26883.

[31] S.P. Gubbels, M. Richardson, D. Trune, D.A. Bascom, M.K. Wax, Tracheal reconstruction with porcine small intestine submucosa in a rabbit model, Otolaryngol. Head Neck Surg. 134 (2006) 1028–1035, https://doi.org/10.1016/j.otohns.2005.12.034.

[32] B.P. Kropp, Small-intestinal submucosa for bladder augmentation: a review of preclinical studies, World J. Urol. 16 (1998) 262–267, https://doi.org/10.1007/s003450050064.

[33] P. Zhao, X. Li, Q. Fang, F. Wang, Q. Ao, X. Wang, X. Tian, H. Tong, S. Bai, J. Fan, Surface modification of small intestine submucosa in tissue engineering, Regen Biomater 7 (2020) 339–348, https://doi.org/10.1093/rb/rbaa014.

[34] J.-C. Luo, W. Chen, X.-H. Chen, T.-W. Qin, Y.-C. Huang, H.-Q. Xie, X.-Q. Li, Z.-Y. Qian, Z.-M. Yang, A multi-step method for preparation of porcine small intestinal submucosa (SIS), Biomaterials 32 (2011) 706–713, https://doi.org/10.1016/j.biomaterials.2010.09.017.

[35] B.S. Kim, S. Das, J. Jang, D.-W. Cho, Decellularized extracellular matrix-based bioinks for engineering tissue- and organ-specific microenvironments, Chem. Rev. 120 (2020) 10608–10661, https://doi.org/10.1021/acs.chemrev.9b00808.

[36] P.M. Crapo, T.W. Gilbert, S.F. Badylak, An overview of tissue and whole organ decellularization processes, Biomaterials 32 (2011) 3233–3243, https://doi.org/10.1016/j.biomaterials.2011.01.057.

[37] Y. Ji, J. Zhou, T. Sun, K. Tang, Z. Xiong, Z. Ren, S. Yao, K. Chen, F. Yang, F. Zhu, X. Guo, Diverse preparation methods for small intestinal submucosa (SIS): decellularization, components, and structure, J. Biomed. Mater. Res. 107 (2019) 689–697, https://doi.org/10.1002/jbm.a.36582.

[38] M. Casarin, T.M. Fortunato, S. Imran, M. Todesco, D. Sandrin, G. Borile, I. Toniolo, M. Marchesan, G. Gerosa, A. Bagno, F. Romanato, E.L. Carniel, A. Morlacco, F. Dal Moro, Porcine small intestinal submucosa (SIS) as a suitable scaffold for the creation of a tissue-engineered urinary conduit: decellularization, biomechanical and biocompatibility characterization using new approaches, Int. J. Mol. Sci. 23 (2022) 2826, https://doi.org/10.3390/ijms23052826.

[39] T. Palmosi, A.M. Tolomeo, C. Cirillo, D. Sandrin, M. Sciro, S. Negrisolo, M. Todesco, F. Caicci, M. Santoro, E. Dal Lago, M. Marchesan, M. Modesti, A. Bagno, F. Romanato, P. Grumati, A. Fabozzo, G. Gerosa, Small intestinal submucosa-derived extracellular matrix as a heterotopic scaffold for cardiovascular applications, Front. Bioeng. Biotechnol. 10 (2022) 1042434, https://doi.org/10.3389/fbioe.2022.1042434.

[40] B. Andrée, A. Bär, A. Haverich, A. Hilfiker, Small intestinal submucosa segments as matrix for tissue engineering: review, Tissue Eng., Part B 19 (2013) 279–291, https://doi.org/10.1089/ten.TEB.2012.0583.

[41] A.D. Janis, C.C. Johnson, D.M. Ernst, A.O. Brightman, Structural characteristics of small intestinal submucosa constructs dictate in vivo incorporation and angiogenic response, J. Biomater. Appl. 26 (2012) 1013–1033, https://doi.org/10.1177/0885328210391688.

[42] S.F. Badylak, D.O. Freytes, T.W. Gilbert, Reprint of: extracellular matrix as a biological scaffold material: structure and function, Acta Biomater. 23 (Suppl) (2015) S17–S26, https://doi.org/10.1016/j.actbio.2015.07.016.

[43] M. Guo, K. Toda, F. Grinnell, Activation of human keratinocyte migration on type I collagen and fibronectin, J. Cell Sci. 96 (Pt 2) (1990) 197–205, https://doi.org/10.1242/jcs.96.2.197.

[44] T. Manon-Jensen, N.G. Kjeld, M.A. Karsdal, Collagen-mediated hemostasis, J. Thromb. Haemostasis 14 (2016) 438–448, https://doi.org/10.1111/jth.13249.

[45] J.P. Hodde, S.F. Badylak, A.O. Brightman, S.L. Voytik-Harbin, Glycosaminoglycan content of small intestinal submucosa: a bioscaffold for tissue replacement, Tissue Eng. 2 (1996) 209–217, https://doi.org/10.1089/ten.1996.2.209.

[46] S.L. Voytik-Harbin, A.O. Brightman, M.R. Kraine, B. Waisner, S.F. Badylak, Identification of extractable growth factors from small intestinal submucosa, J. Cell. Biochem. 67 (1997) 478–491.

[47] B. Brown, K. Lindberg, J. Reing, D.B. Stolz, S.F. Badylak, The basement membrane component of biologic scaffolds derived from extracellular matrix, Tissue Eng. 12 (2006) 519–526, https://doi.org/10.1089/ten.2006.12.519.

[48] H. Xing, H. Lee, L. Luo, T.R. Kyriakides, Extracellular matrix-derived biomaterials in engineering cell function, Biotechnol. Adv. 42 (2020) 107421, https://doi.org/10.1016/j.biotechadv.2019.107421.

[49] S.F. Badylak, T.W. Gilbert, Immune response to biologic scaffold materials, Semin. Immunol. 20 (2008) 109–116, https://doi.org/10.1016/j.smim.2007.11.003.

[50] D.H. Joziasse, J.H. Shaper, E.W. Jabs, N.L. Shaper, Characterization of an alpha 1——3-galactosyltransferase homologue on human chromosome 12 that is organized as a processed pseudogene, J. Biol. Chem. 266 (1991) 6991–6998.

[51] T.B. McPherson, H. Liang, R.D. Record, S.F. Badylak, Galalpha(1,3)Gal epitope in porcine small intestinal submucosa, Tissue Eng. 6 (2000) 233–239, https://doi.org/10.1089/107632700050044416.

[52] R.H. Raeder, S.F. Badylak, C. Sheehan, B. Kallakury, D.W. Metzger, Natural anti-galactose alpha1,3 galactose antibodies delay, but do not prevent the acceptance of extracellular matrix xenografts, Transpl. Immunol. 10 (2002) 15–24, https://doi.org/10.1016/s0966-3274(01)00044-2.

[53] A.J. Allman, T.B. McPherson, S.F. Badylak, L.C. Merrill, B. Kallakury, C. Sheehan, R.H. Raeder, D.W. Metzger, Xenogeneic extracellular matrix grafts elicit a TH2-restricted immune response, Transplantation 71 (2001) 1631–1640, https://doi.org/10.1097/00007890-200106150-00024.

[54] T.W. Gilbert, A.M. Stewart-Akers, S.F. Badylak, A quantitative method for evaluating the degradation of biologic scaffold materials, Biomaterials 28 (2007) 147–150, https://doi.org/10.1016/j.biomaterials.2006.08.022.

[55] R. Rd, H. D, S. C, T. R, R. Fa, E. D, B. Sf, In vivo degradation of 14C-labeled small intestinal submucosa (SIS) when used for urinary bladder repair, Biomaterials 22 (2001), https://doi.org/10.1016/s0142-9612(01)00007-2.

[56] T.W. Gilbert, A.M. Stewart-Akers, A. Simmons-Byrd, S.F. Badylak, Degradation and remodeling of small intestinal submucosa in canine Achilles tendon repair, J. Bone Joint Surg. Am. 89 (2007) 621–630, https://doi.org/10.2106/JBJS.E.00742.

[57] L.-C. Da, Y.-Z. Huang, H.-Q. Xie, B.-H. Zheng, Y.-C. Huang, S.-R. Du, Membranous extracellular matrix-based scaffolds for skin wound healing, Pharmaceutics 13 (2021) 1796, https://doi.org/10.3390/pharmaceutics13111796.

[58] C. Cadena, D.M. Tabima, J.C. Briceno, Tensile mechanical properties of porcine small intestinal submucosa scaffolds: effect of orientation and number of layers, Am. Soc. Artif. Intern. Organs J. 51 (2005) 10A. https://journals.lww.com/asaiojournal/fulltext/2005/03000/tensile_mechanical_properties_of_porcine_small.37.aspx. (Accessed 16 February 2024).

[59] M. Gompelman, S.A.V. van Asten, E.J.G. Peters, Update on the role of infection and biofilms in wound healing: pathophysiology and treatment, Plast. Reconstr. Surg. 138 (2016) 61S, https://doi.org/10.1097/PRS.0000000000002679.

[60] Z. Song, W. Yao, X. Zhang, Y. Dong, Z. Zhang, Y. Huang, W. Jing, L. Sun, Y. Han, F. Hu, Z. Yuan, B. Zhao, P. Wei, X. Zhang, Controlled growth of metal-organic frameworks on small intestinal submucosa for wound repair through combined antibacterial and angiogenic effects, Nano Today 54 (2024) 102060, https://doi.org/10.1016/j.nantod.2023.102060.

[61] B. Han, C. Fan, S. Liu, [Improvement of blood compatibility of small intestinal submucosa used as engineering vascular scaffolds by nano-bionic surface modification], Zhonghua Yixue Zazhi 86 (2006) 2065–2068.

[62] S. Ja, F. Sl, T. Va, B. Jc, M.-C. C, C. Jc, Formulation and characterization of a SIS-based photocrosslinkable bioink, Polymers 11 (2019), https://doi.org/10.3390/polym11030569.

[63] M. Dussoyer, A. Michopoulou, P. Rousselle, Decellularized scaffolds for skin repair and regeneration, Appl. Sci. 10 (2020) 3435, https://doi.org/10.3390/app10103435.

[64] R.S. Kirsner, M.L. Sabolinski, N.B. Parsons, M. Skornicki, W.A. Marston, Comparative effectiveness of a bioengineered living cellular construct vs. a dehydrated human amniotic membrane allograft for the treatment of diabetic foot ulcers in a real world setting, Wound Repair Regen. 23 (2015) 737–744, https://doi.org/10.1111/wrr.12332.

[65] Y.-L. Qiu, X. Chen, Y.-L. Hou, Y.-J. Hou, S.-B. Tian, Y.-H. Chen, L. Yu, M.-H. Nie, X.-Q. Liu, Characterization of different biodegradable scaffolds in tissue engineering, Mol. Med. Rep. 19 (2019) 4043–4056, https://doi.org/10.3892/mmr.2019.10066.

[66] J. Zhang, G.Y. Wang, Y.P. Xiao, L.Y. Fan, Q. Wang, The biomechanical behavior and host response to porcine-derived small intestine submucosa, pericardium and dermal matrix acellular grafts in a rat abdominal defect model, Biomaterials 32 (2011) 7086–7095, https://doi.org/10.1016/j.biomaterials.2011.06.016.

[67] Y. Zhang, C. Zhang, Y. Li, L. Zhou, N. Dan, J. Min, Y. Chen, Y. Wang, Evolution of biomimetic ECM scaffolds from decellularized tissue matrix for tissue engineering: a comprehensive review, Int. J. Biol. Macromol. 246 (2023) 125672, https://doi.org/10.1016/j.ijbiomac.2023.125672.

[68] B.N. Brown, R. Londono, S. Tottey, L. Zhang, K.A. Kukla, M.T. Wolf, K.A. Daly, J. E. Reing, S.F. Badylak, Macrophage phenotype as a predictor of constructive remodeling following the implantation of biologically derived surgical mesh materials, Acta Biomater. 8 (2012) 978–987, https://doi.org/10.1016/j.actbio.2011.11.031.

[69] J. Neill, K. James, W. Lineaweaver, Utilizing biologic assimilation of bovine fetal collagen in staged skin grafting, Ann. Plast. Surg. 68 (2012) 451–456, https://doi.org/10.1097/SAP.0b013e31824189ed.

[70] J.S.A. Neill, W.C. Lineaweaver, Tissue response to bovine fetal collagen extracellular matrix in full-thickness skin wounds, Am. J. Clin. Pathol. 140 (2013) 248–252, https://doi.org/10.1309/AJCPMF3B9XJAKXKM.

[71] A.E. King, A. Paltoo, R.W. Kelly, J.-M. Sallenave, A.D. Bocking, J.R.G. Challis, Expression of natural antimicrobials by human placenta and fetal membranes, Placenta 28 (2007) 161–169, https://doi.org/10.1016/j.placenta.2006.01.006.

[72] H. Xiao, X. Chen, X. Liu, G. Wen, Y. Yu, Recent advances in decellularized biomaterials for wound healing, Mater. Today Bio 19 (2023) 100589, https://doi.org/10.1016/j.mtbio.2023.100589.

[73] N.E. Liang, M.F. Griffin, C.E. Berry, J.B. Parker, M.A. Downer, D.C. Wan, M. T. Longaker, Attenuating chronic fibrosis: decreasing foreign body response with acellular dermal matrix, Tissue Eng., Part B 29 (2023) 671–680, https://doi.org/10.1089/ten.TEB.2023.0060.

[74] S. Doudi, M. Barzegar, E.A. Taghavi, M. Eini, A. Ehterami, K. Stokes, J. S. Alexander, M. Salehi, Applications of acellular human amniotic membrane in regenerative medicine, Life Sci. 310 (2022) 121032, https://doi.org/10.1016/j.lfs.2022.121032.

[75] A.-M. Kajbafzadeh, N. Javan-Farazmand, M. Monajemzadeh, A. Baghayee, Determining the optimal decellularization and sterilization protocol for preparing a tissue scaffold of a human-sized liver tissue, Tissue Eng. C Methods 19 (2013) 642–651, https://doi.org/10.1089/ten.TEC.2012.0334.

[76] A.A. Golebiowska, J.T. Intravaia, V.M. Sathe, S.G. Kumbar, S.P. Nukavarapu, Decellularized extracellular matrix biomaterials for regenerative therapies: advances, challenges and clinical prospects, Bioact. Mater. 32 (2024) 98–123, https://doi.org/10.1016/j.bioactmat.2023.09.017.

[77] J. Hodde, A. Janis, D. Ernst, D. Zopf, D. Sherman, C. Johnson, Effects of sterilization on an extracellular matrix scaffold: part I. Composition and matrix architecture, J. Mater. Sci. Mater. Med. 18 (2007) 537–543, https://doi.org/10.1007/s10856-007-2300-x.

[78] J. Hodde, A. Janis, M. Hiles, Effects of sterilization on an extracellular matrix scaffold: part II. Bioactivity and matrix interaction, J. Mater. Sci. Mater. Med. 18 (2007) 545–550, https://doi.org/10.1007/s10856-007-2301-9.

[79] X. Miao, S. Yang, J. Zhu, Z. Gong, D. Wu, J. Hong, K. Cai, J. Wang, X. Fang, J. Lu, G. Jiang, Bioactive mineralized small intestinal submucosa acellular matrix/PMMA bone cement for vertebral bone regeneration, Regen Biomater 10 (2023), https://doi.org/10.1093/rb/rbad040 rbad040.

[80] Q.-Y. Zhang, J. Tan, R. Nie, Y.-T. Song, X.-L. Zhou, Z.-Y. Feng, K. Huang, C.-Y. Zou, Q.-J. Yuan, L.-M. Zhao, X.-Z. Zhang, Y.-L. Jiang, L.-M. Liu, J. Li-Ling, H.-Q. Xie, Acceleration of wound healing by composite small intestinal submucosa hydrogels through immunomodulation, Compos. B Eng. 254 (2023) 110550, https://doi.org/10.1016/j.compositesb.2023.110550.

[81] H. Singh, S.D. Purohit, R. Bhaskar, I. Yadav, S. Bhushan, M.K. Gupta, N.C. Mishra, Curcumin in decellularized goat small intestine submucosa for wound healing and skin tissue engineering, J. Biomed. Mater. Res. B Appl. Biomater. 110 (2022) 210–219, https://doi.org/10.1002/jbm.b.34903.

[82] B. Nasiri, S. Row, J. Randall J. Smith, D.D. Swartz, S.T. Andreadis, Cell-free vascular grafts that grow with the host, Adv. Funct. Mater. 30 (2020), https://doi.org/10.1002/adfm.202005769.

[83] K. Kim, H. Kim, S. Do, H. Kim, Potential of aligned electrospun PLGA/SIS blended nanofibrous membrane for tendon tissue engineering, Polymers 15 (2023) 2313, https://doi.org/10.3390/polym15102313.

[84] X. Xie, W. Wang, J. Cheng, H. Liang, Z. Lin, T. Zhang, Y. Lu, Q. Li, Bilayer pifithrin-α loaded extracellular matrix/PLGA scaffolds for enhanced vascularized bone formation, Colloids Surf. B Biointerfaces 190 (2020) 110903, https://doi.org/10.1016/j.colsurfb.2020.110903.

[85] O. Syed, J.-H. Kim, Z. Keskin-Erdogan, R.M. Day, A. El-Fiqi, H.-W. Kim, J. C. Knowles, SIS/aligned fibre scaffold designed to meet layered oesophageal tissue complexity and properties, Acta Biomater. 99 (2019) 181–195, https://doi.org/10.1016/j.actbio.2019.08.015.

[86] M.J. Kim, Y.B. Ji, J.Y. Seo, S.H. Park, J.H. Kim, B.H. Min, M.S. Kim, Substance P-loaded electrospun small intestinal submucosa/poly(ε-caprolactone)-ran-poly(l-lactide) sheet to facilitate wound healing through MSC recruitment, J. Mater. Chem. B 7 (2019) 7599–7611, https://doi.org/10.1039/c9tb01532a.

[87] Y. Su, B. Ye, L. Zeng, Z. Xiong, T. Sun, K. Chen, Q. Ding, W. Su, X. Jing, Q. Gao, G. Huang, Y. Wan, X. Yang, X. Guo, Small intestinal submucosa biomimetic periosteum promotes bone regeneration, Membranes 12 (2022) 719, https://doi.org/10.3390/membranes12070719.

[88] L. Yang, S. Jin, L. Shi, I. Ullah, K. Yu, W. Zhang, L. Bo, X. Zhang, X. Guo, Cryogenically 3D printed biomimetic scaffolds containing decellularized small intestinal submucosa and Sr2+/Fe3+ co-substituted hydroxyapatite for bone tissue engineering, Chem. Eng. J. 431 (2022) 133459, https://doi.org/10.1016/j.cej.2021.133459.
[89] Y. Hu, B. Wu, Y. Xiong, R. Tao, A.C. Panayi, L. Chen, W. Tian, H. Xue, L. Shi, X. Zhang, L. Xiong, B. Mi, G. Liu, Cryogenic 3D printed hydrogel scaffolds loading exosomes accelerate diabetic wound healing, Chem. Eng. J. 426 (2021) 130634, https://doi.org/10.1016/j.cej.2021.130634.
[90] S. Wang, W. Wu, Y. Liu, X. Wang, L. Tang, P. You, J. Han, B. Li, Y. Zhang, M. Wang, Bone augmentation of peri-implant dehiscence defects using multilaminated small intestinal submucosa as a barrier membrane: an experimental study in dogs, BioMed Res. Int. 2019 (2019) 8962730, https://doi.org/10.1155/2019/8962730.
[91] B.A. Gonzalez, E. Pour Issa, O.V. Mankame, J. Bustillos, A. Cuellar, A. J. Rodriguez, F. Scholl, S. Bibevski, L. Hernandez, V. Brehier, M. Casares, K. Rivas-Wagner, P. Morales, J. Lopez, J. Wagner, J. Bibevski, A. Agarwal, F. George, S. Ramaswamy, Porcine small intestinal submucosa mitral valve material responses support acute somatic growth, Tissue Eng. 26 (2020) 475–489, https://doi.org/10.1089/ten.TEA.2019.0220. Part A.
[92] B. Li, Y. Liu, Y. Zhou, P. You, M. Wang, L. Tang, Y. Deng, Development of a novel extracellular matrix membrane with an asymmetric structure for guided bone regeneration, Mater. Lett. 274 (2020) 127926, https://doi.org/10.1016/j.matlet.2020.127926.
[93] X. Bi, L. Li, Z. Mao, B. Liu, L. Yang, W. He, Y. Fan, X. Li, The effects of silk layer-by-layer surface modification on the mechanical and structural retention of extracellular matrix scaffolds, Biomater. Sci. 8 (2020) 4026–4038, https://doi.org/10.1039/d0bm00448k.
[94] L. Wang, F. Liu, X. Zhai, W. Dong, W. Wei, Z. Hu, An adhesive gelatin-coated small intestinal submucosa composite hydrogel dressing aids wound healing, Int. J. Biol. Macromol. 241 (2023) 124622, https://doi.org/10.1016/j.ijbiomac.2023.124622.
[95] H. Cao, L. Yang, R. Tian, H. Wu, Z. Gu, Y. Li, Versatile polyphenolic platforms in regulating cell biology, Chem. Soc. Rev. 51 (2022) 4175–4198, https://doi.org/10.1039/d1cs01165k.
[96] X. Zhang, Z. Li, P. Yang, G. Duan, X. Liu, Z. Gu, Y. Li, Polyphenol scaffolds in tissue engineering, Mater. Horiz. 8 (2021) 145–167, https://doi.org/10.1039/d0mh01317j.
[97] L.-P. Huang, Y. Liu, Q.-J. Li, W.-Q. Zhang, C.-Y. Wu, L.-M. Zhao, H.-Q. Xie, A modified small intestinal submucosa patch with multifunction to promote scarless repair and reinvigoration of urethra, Adv. Healthcare Mater. 12 (2023) e2300519, https://doi.org/10.1002/adhm.202300519.
[98] X.-Z. Zhang, Y.-L. Jiang, J.-G. Hu, L.-M. Zhao, Q.-Z. Chen, Y. Liang, Y. Zhang, X.-X. Lei, R. Wang, Y. Lei, Q.-Y. Zhang, J. Li-Ling, H.-Q. Xie, Procyanidins-crosslinked small intestine submucosa: a bladder patch promotes smooth muscle regeneration and bladder function restoration in a rabbit model, Bioact. Mater. 6 (2020) 1827–1838, https://doi.org/10.1016/j.bioactmat.2020.11.023.
[99] Z. Sun, H. Xiong, T. Lou, W. Liu, Y. Xu, S. Yu, H. Wang, W. Liu, L. Yang, C. Zhou, C. Fan, Multifunctional extracellular matrix hydrogel with self-healing properties and promoting angiogenesis as an immunoregulation platform for diabetic wound healing, Gels 9 (2023), https://doi.org/10.3390/gels9050381.
[100] Y.-T. Song, L. Dong, J.-G. Hu, P.-C. Liu, Y.-L. Jiang, L. Zhou, M. Wang, J. Tan, Y.-X. Li, Q.-Y. Zhang, C.-Y. Zou, X.-Z. Zhang, L.-M. Zhao, R. Nie, Y. Zhang, J. Li-Ling, H.-Q. Xie, Application of genipin-crosslinked small intestine submucosa and urine-derived stem cells for the prevention of intrauterine adhesion in a rat model, Compos. B Eng. 250 (2023) 110461, https://doi.org/10.1016/j.compositesb.2022.110461.
[101] K.H. Hillebrandt, H. Everwien, N. Haep, E. Keshi, J. Pratschke, I.M. Sauer, Strategies based on organ decellularization and recellularization, Transpl. Int. 32 (2019) 571–585, https://doi.org/10.1111/tri.13462.
[102] M. Parmaksiz, A.E. Elçin, Y.M. Elçin, Decellularized bSIS-ECM as a regenerative biomaterial for skin wound repair, Methods Mol. Biol. 1879 (2019) 175–185, https://doi.org/10.1007/7651_2018_147.
[103] Q. M, H. M, W. H, Z. H, W. C, H. Q, Umbilical cord mesenchymal stem cells seeded on small intestinal submucosa to repair the uterine wall injuries, tissue engineering, Methods 28 (2022), https://doi.org/10.1089/ten.TEC.2022.0007. Part C.
[104] B.A. Gonzalez, A. Herrera, C. Ponce, M. Gonzalez Perez, C.-P.D. Hsu, A. Mirza, M. Perez, S. Ramaswamy, Stem cell-secreted allogeneic elastin-rich matrix with subsequent decellularization for the treatment of critical valve diseases in the young, Bioengineering 9 (2022) 587, https://doi.org/10.3390/bioengineering9100587.
[105] Y. Zhang, S. Shi, Q. Xu, Q. Zhang, R.M. Shanti, A.D. Le, SIS-ECM laden with GMSC-derived exosomes promote taste bud regeneration, J. Dent. Res. 98 (2019) 225–233, https://doi.org/10.1177/0022034518804531.
[106] M.I. Bury, N.J. Fuller, R.M. Sturm, R.R. Rabizadeh, B.G. Nolan, M. Barac, S. S. Edassery, Y.Y. Chan, A.K. Sharma, The effects of bone marrow stem and progenitor cell seeding on urinary bladder tissue regeneration, Sci. Rep. 11 (2021) 2322, https://doi.org/10.1038/s41598-021-81939-5.
[107] X. Wang, G. Wang, S. Zingales, B. Zhao, Biomaterials enabled cell-free strategies for endogenous bone regeneration, Tissue Eng., Part B 24 (2018) 463–481, https://doi.org/10.1089/ten.TEB.2018.0012.
[108] P. Zhao, Q. Fang, D. Gao, Q. Wang, Y. Cheng, Q. Ao, X. Wang, X. Tian, Y. Zhang, H. Tong, N. Yan, X. Hu, J. Fan, Klotho functionalization on vascular graft for improved patency and endothelialization, Biomater. Adv. 133 (2022) 112630, https://doi.org/10.1016/j.msec.2021.112630.
[109] B.S. Kim, Y.W. Kwon, J.-S. Kong, G.T. Park, G. Gao, W. Han, M.-B. Kim, H. Lee, J. H. Kim, D.-W. Cho, 3D cell printing of in vitro stabilized skin model and in vivo pre-vascularized skin patch using tissue-specific extracellular matrix bioink: a step towards advanced skin tissue engineering, Biomaterials 168 (2018) 38–53, https://doi.org/10.1016/j.biomaterials.2018.03.040.
[110] Z. Zeng, M. Zhu, L. Chen, Y. Zhang, T. Lu, Y. Deng, W. Ma, J. Xu, C. Huang, R. Xiong, Design the molecule structures to achieve functional advantages of hydrogel wound dressings: advances and strategies, Compos. B Eng. 247 (2022) 110313, https://doi.org/10.1016/j.compositesb.2022.110313.
[111] K. Järbrink, G. Ni, H. Sönnergren, A. Schmidtchen, C. Pang, R. Bajpai, J. Car, The humanistic and economic burden of chronic wounds: a protocol for a systematic review, Syst. Rev. 6 (2017) 15, https://doi.org/10.1186/s13643-016-0400-8.
[112] L.A. DiPietro, Angiogenesis and wound repair: when enough is enough, J. Leukoc. Biol. 100 (2016) 979–984, https://doi.org/10.1189/jlb.4MR0316-102R.
[113] S. Ma, Y. Yang, Y. Mu, H. Peng, P. Wei, W. Jing, C. Peng, X. Liu, B. Zhao, M. Cai, Z. Liu, X. Yu, J. Deng, Modification of the small intestinal submucosa membrane with oligopeptides screened from intrinsically disordered regions to promote angiogenesis and accelerate wound healing, Biomater. Adv. 148 (2023) 213360, https://doi.org/10.1016/j.bioadv.2023.213360.
[114] S. Ma, H. Hu, J. Wu, X. Li, X. Ma, Z. Zhao, Z. Liu, C. Wu, B. Zhao, Y. Wang, W. Jing, Functional extracellular matrix hydrogel modified with MSC-derived small extracellular vesicles for chronic wound healing, Cell Prolif. 55 (2022), https://doi.org/10.1111/cpr.13196.
[115] Y. Su, X. Zhang, G. Ren, Z. Zhang, Y. Liang, S. Wu, J. Shen, In situ implantable three-dimensional extracellular matrix bioactive composite scaffold for postoperative skin cancer therapy, Chem. Eng. J. 400 (2020) 125949, https://doi.org/10.1016/j.cej.2020.125949.
[116] Y. Wang, L. Hou, Y. Huang, P. Wei, L. Sun, Y. Zhang, X. Yu, S. Ma, W. Jing, B. Zhao, H. Ma, Decorated small intestinal submucosa (SIS) based bio-patch with anti-fouling and vascularized capacity to accelerate chronic wound regeneration via TGF-β and MAPK pathway, Appl. Surf. Sci. 614 (2023) 156185, https://doi.org/10.1016/j.apsusc.2022.156185.
[117] S. Ma, Y. Zhao, Y. Yang, Y. Mu, L. Zhang, J. Wu, R. Li, X. Bian, P. Wei, W. Jing, B. Zhao, Z. Liu, J. Deng, Asymmetric SIS membranes specifically loaded with exosomes through the modification of engineered recombinant peptides for guide bone regeneration, Compos. B Eng. 232 (2022) 109571, https://doi.org/10.1016/j.compositesb.2021.109571.
[118] J. Tan, Q.-Y. Zhang, Y.-T. Song, K. Huang, Y.-L. Jiang, J. Chen, R. Wang, C.-Y. Zou, Q.-J. Li, B.-Q. Qin, N. Sheng, R. Nie, Z.-Y. Feng, D.-Z. Yang, W.-H. Yi, H.-Q. Xie, Accelerated bone defect regeneration through sequential activation of the M1 and M2 phenotypes of macrophages by a composite BMP-2@SIS hydrogel: an immunomodulatory perspective, Compos. B Eng. 243 (2022) 110149, https://doi.org/10.1016/j.compositesb.2022.110149.
[119] R. Kheirjou, J.S. Rad, A.F. Khosroshahi, S. Davaran, L. Roshangar, Evaluation the ability of acellular ovine small intestine submucosa to load and release of mineral pitch and its anti-inflammatory effects, Cell Tissue Bank. 23 (2022) 541–555, https://doi.org/10.1007/s10561-021-09985-x.
[120] X.-Y. Chen, Y. Wang, S.-Q. Ma, Y.-Q. Huang, W. Jing, P.-F. Wei, X.-Q. Yu, B. Zhao, Mechanically active small intestinal submucosa hydrogel for accelerating chronic wound healing, J. Mater. Chem. B 10 (2022) 6279–6286, https://doi.org/10.1039/d2tb01355j.
[121] L. Yang, Y. Liu, L. Sun, C. Zhao, G. Chen, Y. Zhao, Biomass microcapsules with stem cell encapsulation for bone repair, Nano-Micro Lett. 14 (2021) 4, https://doi.org/10.1007/s40820-021-00747-8.
[122] F.R. Maia, A.R. Bastos, J.M. Oliveira, V.M. Correlo, R.L. Reis, Recent approaches towards bone tissue engineering, Bone 154 (2022) 116256, https://doi.org/10.1016/j.bone.2021.116256.
[123] N.G. Schott, N.E. Friend, J.P. Stegemann, Coupling osteogenesis and vasculogenesis in engineered orthopedic tissues, Tissue Eng., Part B 27 (2021) 199–214, https://doi.org/10.1089/ten.teb.2020.0132.
[124] Z. Liu, P. Wei, Q. Cui, Y. Mu, Y. Zhao, J. Deng, M. Zhi, Y. Wu, W. Jing, X. Liu, J. Zhao, B. Zhao, Guided bone regeneration with extracellular matrix scaffold of small intestinal submucosa membrane, J. Biomater. Appl. 37 (2022) 805–813, https://doi.org/10.1177/08853282221114450.
[125] W.L. Chung, B.N. Brown, A.J. Almarza, Decellularized small intestine submucosa device for temporomandibular joint meniscus repair: acute timepoint safety study, PLoS One 17 (2022) e0273336, https://doi.org/10.1371/journal.pone.0273336.
[126] B.N. Brown, W.L. Chung, J. Lowe, S.T. LoPresti, J. Cheetham, A.J. Almarza, S. F. Badylak, Inductive remodeling of extracellular matrix scaffolds in the temporomandibular joint of pigs, Tissue Eng. 28 (2022) 447–457, https://doi.org/10.1089/ten.TEA.2021.0123.
[127] C. Meng, W. Su, M. Liu, S. Yao, Q. Ding, K. Yu, Z. Xiong, K. Chen, X. Guo, L. Bo, T. Sun, Controlled delivery of bone morphogenic protein-2-related peptide from mineralised extracellular matrix-based scaffold induces bone regeneration, Mater. Sci. Eng., C 126 (2021) 112182, https://doi.org/10.1016/j.msec.2021.112182.
[128] Z. Mosala Nezhad, A. Poncelet, L. de Kerchove, P. Gianello, C. Fervaille, G. El Khoury, Small intestinal submucosa extracellular matrix (CorMatrix®) in cardiovascular surgery: a systematic review, Interact. Cardiovasc. Thorac. Surg. 22 (2016) 839–850, https://doi.org/10.1093/icvts/ivw020.
[129] S.-Y. Wang, J.-W. Sang, W. Ding, T.-W. Qin, L. Bai, J. Zhang, J.-C. Luo, The cytoptrotection of small intestinal submucosa-derived gel in HL-1 cells during hypoxia/reoxygenation-induced injury, J. Tissue Eng. Regen. Med. 13 (2019) 1346–1361, https://doi.org/10.1002/term.2878.
[130] S.F. Badylak, The extracellular matrix as a biologic scaffold material, Biomaterials 28 (2007) 3587–3593, https://doi.org/10.1016/j.biomaterials.2007.04.043.

[131] T. Holubec, E. Caliskan, S.H. Sündermann, C.T. Starck, A. Plass, D. Bettex, V. Falk, F. Maisano, Use of extracellular matrix patches in cardiac surgery, J. Card. Surg. 30 (2015) 145–148, https://doi.org/10.1111/jocs.12494.
[132] X. Yang, S. Chen, J. Chen, Y. Liu, Y. Bai, S. Yin, D. Quan, The different effect of decellularized myocardial matrix hydrogel and decellularized small intestinal submucosa matrix hydrogel on cardiomyocytes and ischemic heart, Appl. Sci. 11 (2021) 7768, https://doi.org/10.3390/app11177768.
[133] B.A. Gonzalez, M. Perez Gonzalez, F. Scholl, S. Bibevski, E. Ladich, J. Bibevski, P. Morales, J. Lopez, M. Casares, V. Brehier, L. Hernandez, S. Ramaswamy, De novo valve tissue morphology following bioscaffold mitral valve replacement in a juvenile non-human primate model, Bioengineering 8 (2021) 100, https://doi.org/10.3390/bioengineering8070100.
[134] F. Q, G. T, F. J, Z. Y, W. Y, Z. Y, Z. P, Evaluation of a hybrid small caliber vascular graft in a rabbit model, J. Thorac. Cardiovasc. Surg. 159 (2020), https://doi.org/10.1016/j.jtcvs.2019.02.083.
[135] S. Shamout, S. Nazha, A. Dragomir, R. Baverstock, J. Corcos, L. Campeau, A cost-effectiveness analysis of bladder management strategies in neurogenic lower urinary tract dysfunction after spinal cord injury: a publicly funded health care perspective, Spinal Cord 61 (2023) 269–275, https://doi.org/10.1038/s41393-023-00883-5.
[136] K. Ławkowska, C. Rosenbaum, P. Petrasz, L. Kluth, K. Koper, T. Drewa, M. Pokrywczynska, J. Adamowicz, Trauma and Reconstructive Urology Working Party of the European Association of Urology Young Academic Urologists, Tissue engineering in reconstructive urology-The current status and critical insights to set future directions-critical review, Front. Bioeng. Biotechnol. 10 (2022) 1040987, https://doi.org/10.3389/fbioe.2022.1040987.
[137] Y.-T. Song, Y.-Q. Li, M.-X. Tian, J.-G. Hu, X.-R. Zhang, P.-C. Liu, X.-Z. Zhang, Q.-Y. Zhang, L. Zhou, L.-M. Zhao, J. Li-Ling, H.-Q. Xie, Application of antibody-conjugated small intestine submucosa to capture urine-derived stem cells for bladder repair in a rabbit model, Bioact. Mater. 14 (2022) 443–455, https://doi.org/10.1016/j.bioactmat.2021.11.017.
[138] L. Peng, X. Jin, Q. He, X. Gao, W. Wang, X. Zeng, H. Shen, D. Luo, Remodelling landscape of tissue-engineered bladder with porcine small intestine submucosa using single-cell RNA sequencing, Cell Prolif. 56 (2022) e13343, https://doi.org/10.1111/cpr.13343.
[139] S. Sharma, S. Rajani, J. Hui, A. Chen, T. Bivalacqua, A. Singh, Development of enzymatic-resistant and compliant decellularized extracellular matrixes via aliphatic chain modification for bladder tissue engineering, ACS Appl. Mater. Interfaces 14 (2022) 37301–37315, https://doi.org/10.1021/acsami.2c06865.
[140] E. Dreisler, J.J. Kjer, Asherman's syndrome: current perspectives on diagnosis and management, Int. J. Womens Health 11 (2019) 191–198, https://doi.org/10.2147/IJWH.S165474.
[141] Y. Xiao, Y. Tian, J. Zhang, Q. Li, W. Shi, X. Huang, Small intestinal submucosa promotes angiogenesis via the Hippo pathway to improve vaginal repair, Biomol. Biomed. 23 (2023) 838–847, https://doi.org/10.17305/bb.2023.9052.
[142] X. Guo, H. Lv, Z. Fan, K. Duan, J. Liang, L. Zou, H. Xue, D. Huang, Y. Wang, M. Tan, Effects of hypoxia on Achilles tendon repair using adipose tissue-derived mesenchymal stem cells seeded small intestinal submucosa, J. Orthop. Surg. Res. 16 (2021) 570, https://doi.org/10.1186/s13018-021-02713-x.
[143] X. Mao, L. Yao, M. Li, X. Zhang, B. Weng, W. Zhu, R. Ni, K. Chen, L. Yi, J. Zhao, H. Mao, Enhancement of tendon repair using tendon-derived stem cells in small intestinal submucosa via M2 macrophage polarization, Cells 11 (2022) 2770, https://doi.org/10.3390/cells11172770.
[144] X. Zhang, Z. Fang, E. Cho, K. Huang, J. Zhao, J. Jiang, X. Huangfu, Use of a novel, reinforced, low immunogenic, porcine small intestine submucosa patch to repair a supraspinatus tendon defect in a rabbit model, BioMed Res. Int. 2019 (2019) 9346567, https://doi.org/10.1155/2019/9346567.
[145] C. Galvez Alegria, G. Gundogdu, X. Yang, K. Costa, J.R. Mauney, Evaluation of acellular bilayer silk fibroin grafts for onlay tracheoplasty in a rat defect model, Otolaryngol. Head Neck Surg. 160 (2019) 310–319, https://doi.org/10.1177/0194599818802267.
[146] N.-K. Viet-Nhi, Y.-C. Chen, L.H. Dang, H. Tseng, S.-H. Hung, Degassing a decellularized scaffold enhances wound healing and reduces fibrosis during tracheal defect reconstruction: a preliminary animal study, J. Funct. Biomater. 14 (2023) 147, https://doi.org/10.3390/jfb14030147.
[147] G. Cao, W. He, Y. Fan, X. Li, Exploring the match between the degradation of the ECM-based composites and tissue remodeling in a full-thickness abdominal wall defect model, Biomater. Sci. 9 (2021) 7895–7910, https://doi.org/10.1039/d1bm01096d.
[148] L. Zhang, S. Ma, P. Wei, Y. Zhao, Y. Mu, J. Wu, W. Jing, B. Zhao, J. Deng, Z. Liu, Small intestinal submucosa membrane modified by fusion peptide-mediated extracellular vesicles to promote tissue regeneration, Adv. Healthcare Mater. 10 (2021) e2101298, https://doi.org/10.1002/adhm.202101298.
[149] R. Zhukauskas, D.N. Fischer, C. Deister, N.Z. Alsmadi, D. Mercer, A comparative study of porcine small intestine submucosa and cross-linked bovine type I collagen as a nerve conduit, J. Hand Surg. Glob. Online 3 (2021) 282–288, https://doi.org/10.1016/j.jhsg.2021.06.006.
[150] T.R. Kamal, A. Tyraskis, H. Ghattaura, A. Fitchie, K. Lakhoo, Synthetic versus biological patches for cdh: a comparison of recurrence rates and adverse events, systematic review, and meta-analysis, Eur. J. Pediatr. Surg. 33 (2023) 198–209, https://doi.org/10.1055/s-0042-1748530.
[151] C. Zang, H. Xian, H. Zhang, M. Che, Y. Chen, F. Zhang, R. Cong, Clinical outcomes of a novel porcine small intestinal submucosa patch for full-thickness hand skin defects: a retrospective investigation, J. Orthop. Surg. Res. 18 (2023) 50, https://doi.org/10.1186/s13018-023-03531-z.
[152] X. Zhang, J. Qiu, J. Ding, K. Hua, Comparison of neovaginoplasty using acellular porcine small intestinal submucosa graft or Interceed in patients with Mayer-Rokitansky-Küster-Hauser syndrome, Arch. Gynecol. Obstet. 300 (2019) 1633–1636, https://doi.org/10.1007/s00404-019-05352-0.
[153] F. Zhang, L. Liao, Long-term follow-up of neurogenic bladder patients after bladder augmentation with small intestinal submucosa, World J. Urol. 38 (2020) 2279–2288, https://doi.org/10.1007/s00345-019-03008-x.
[154] O.E. Speed, A. Bareiss, V.A. Patel, A. Mangan, J. Dornhoffer, R.A. Saadi, Otologic use of porcine small intestinal submucosal graft (biodesign): a MAUDE database review, Am. J. Otolaryngol. 44 (2023) 103961, https://doi.org/10.1016/j.amjoto.2023.103961.
[155] H. Zhou, Y. Shen, Z. Zhang, X. Liu, J. Zhang, J. Chen, Comparison of outcomes of ventral hernia repair using different meshes: a systematic review and network meta-analysis, Hernia 26 (2022) 1561–1571, https://doi.org/10.1007/s10029-022-02652-4.
[156] Q. Zhou, X. Zhang, Y. Li, K. Hua, J. Ding, Comparison of Sheares vaginoplasty, vaginoplasty using acellular porcine small intestinal submucosa graft and laparoscopic peritoneal vaginoplasty in patients with Mayer-Rokitansky-Küster-Hauser syndrome, Int. Urogynecol. J. 34 (2023) 499–505, https://doi.org/10.1007/s00192-022-05163-z.
[157] F. Cour, P. Munier, K. Kaulanjan, A. Vidart, P.-O. Bosset, Y. Neuzillet, Small intestinal submucosa xenograft to manage lower urinary tract prostheses perforation: a new path? Int. Urogynecol. J. 33 (2022) 627–635, https://doi.org/10.1007/s00192-021-04771-5.
[158] K.A. Derwin, A.R. Baker, R.K. Spragg, D.R. Leigh, J.P. Iannotti, Commercial extracellular matrix scaffolds for rotator cuff tendon repair. Biomechanical, biochemical, and cellular properties, J. Bone Joint Surg. Am. 88 (2006) 2665–2672, https://doi.org/10.2106/JBJS.E.01307.
[159] R. Simman, Role of small intestinal submucosa extracellular matrix in advanced regenerative wound therapy, J. Wound Care 32 (2023) S3–S10, https://doi.org/10.12968/jowc.2023.32.Sup1a.S3.
[160] M. Sofer, E. Rowe, D.M. Forder, J.D. Denstedt, Ureteral segmental replacement using multilayer porcine small-intestinal submucosa, J. Endourol. 16 (2002) 27–31, https://doi.org/10.1089/089277902753483682.
[161] C.L. Gilbert, J. Gnanapragasam, R. Benhaggen, W.M. Novick, Novel use of extracellular matrix graft for creation of pulmonary valved conduit, World J. Pediatr. Congenit. Heart Surg. 2 (2011) 495–501, https://doi.org/10.1177/2150135111406142.
[162] A.J. Eggink, L.a.J. Roelofs, W.F.J. Feitz, R.M.H. Wijnen, R.A. Mullaart, J. A. Grotenhuis, T.H. van Kuppevelt, M.M.Y. Lammens, A.J. Crevels, A. Hanssen, P. P. van den Berg, In utero repair of an experimental neural tube defect in a chronic sheep model using biomatrices, Fetal Diagn. Ther. 20 (2005) 335–340, https://doi.org/10.1159/000086808.
[163] N. Bryan, H. Ashwin, N. Smart, Y. Bayon, N. Scarborough, J.A. Hunt, The innate oxygen dependant immune pathway as a sensitive parameter to predict the performance of biological graft materials, Biomaterials 33 (2012) 6380–6392, https://doi.org/10.1016/j.biomaterials.2012.05.058.
[164] D.A. Coons, F. Alan Barber, Tendon graft substitutes-rotator cuff patches, Sports Med. Arthrosc. Rev. 14 (2006) 185–190, https://doi.org/10.1097/00132585-200609000-00011.
[165] F.A. Barber, M.A. Herbert, D.A. Coons, Tendon augmentation grafts: biomechanical failure loads and failure patterns, Arthroscopy 22 (2006) 534–538, https://doi.org/10.1016/j.arthro.2005.12.021.
[166] B. Sf, L. Gc, C. A, G. La, Small intestinal submucosa as a large diameter vascular graft in the dog, J. Surg. Res. 47 (1989), https://doi.org/10.1016/0022-4804(89)90050-4.
[167] J.A. Niezgoda, C.C. Van Gils, R.G. Frykberg, J.P. Hodde, Randomized clinical trial comparing OASIS Wound Matrix to Regranex Gel for diabetic ulcers, Adv. Skin Wound Care 18 (2005) 258–266, https://doi.org/10.1097/00129334-200506000-00012.
[168] E.N. Mostow, G.D. Haraway, M. Dalsing, J.P. Hodde, D. King, OASIS Venus Ulcer Study Group, Effectiveness of an extracellular matrix graft (OASIS Wound Matrix) in the treatment of chronic leg ulcers: a randomized clinical trial, J. Vasc. Surg. 41 (2005) 837–843, https://doi.org/10.1016/j.jvs.2005.01.042.
[169] M. Brown-Etris, C.T. Milne, J.P. Hodde, An extracellular matrix graft (Oasis® wound matrix) for treating full-thickness pressure ulcers: a randomized clinical trial, J. Tissue Viability 28 (2019) 21–26, https://doi.org/10.1016/j.jtv.2018.11.001.
[170] T.J. Schnoeller, R. de Petriconi, R. Hefty, F. Jentzmik, S. Waalkes, F. Zengerling, M. Schrader, A.J. Schrader, Partial nephrectomy using porcine small intestinal submucosa, World J. Surg. Oncol. 9 (2011) 126, https://doi.org/10.1186/1477-7819-9-126.
[171] V. Alexandridis, P. Teleman, M. Rudnicki, Efficacy and safety of pelvic organ prolapse surgery with porcine small intestinal submucosa graft implantation, Eur. J. Obstet. Gynecol. Reprod. Biol. 267 (2021) 18–22, https://doi.org/10.1016/j.ejogrb.2021.10.011.
[172] L. Sun, J. Chen, Y. Shen, Randomized controlled trial of lichtenstein repair of indirect inguinal hernias with two biologic meshes from porcine small intestine submucosa, Therapeut. Clin. Risk Manag. 15 (2019) 1277–1282, https://doi.org/10.2147/TCRM.S208185.