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Recent advances and future directions in urinary system tissue engineering

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ABSTRACT

Recent advancements in tissue engineering offer promising solutions for the repair and reconstruction of the urinary system, particularly in cases of urinary organ injuries. Historically, autologous tissue grafts and allografts have been the primary options for repairing damaged tissues. However, these approaches often lead to complications such as immune rejection, donor site morbidity, and functional limitations. Tissue engineering provides a more sustainable alternative by leveraging the potential of cells, bioactive scaffolds, and growth factors to regenerate and repair damaged tissues. This approach aims not only to restore tissue structure but also to enhance functional recovery. Key challenges in the field include achieving adequate vascularization, overcoming immune responses, and ensuring long-term tissue integration. Recent innovations, such as 3D bioprinting, stem cell-based therapies, and the development of novel biomaterials, show great promise in addressing these challenges. This review explores the current state of tissue engineering applications in the urological system, focusing on the regeneration of the bladder, urethra, and kidneys. We discuss recent breakthroughs, ongoing clinical trials, and emerging technologies, as well as the potential for these approaches to improve clinical outcomes. Finally, we outline critical future directions of tissue engineering in urology, emphasizing the need for interdisciplinary collaboration to overcome existing barriers and accelerate clinical translation.

1. Introduction

The urinary system consists of the kidneys, ureters, bladder, and urethra. Its primary function is to excrete waste products generated during the body's metabolic processes, thereby facilitating their removal from the body. The urine produced by the kidneys travels through the ureter to the bladder for temporary storage. Once a sufficient amount of urine has accumulated, it is expelled from the body via the urethra. Therefore, the urinary system is responsible for all aspects of urine production, transport through the ureter, storage in the bladder, and elimination via urination. Due to the synergistic interaction of physiological functions, the urinary system displays similar structural and functional characteristics. Specifically, the renal pelvis, ureter, bladder, and urethra all contain migratory epithelium, a feature unique to the urinary system.

Reconstruction or regeneration of urinary tissues is essential for addressing various disorders. Due to the unique structural and functional characteristics of urinary organs, there is a substantial clinical demand for tissue-engineered substitutes. For example, bladder reconstruction is critical for restoring urinary storage and capacity in cases of bladder dysfunction resulting from spinal cord injury, trauma, congenital malformations, malignant tumors, and other conditions [26,27]. Currently, the most effective approach for bladder replacement and enlargement involves the implantation of intestinal segments. However, this method is associated with significant complications, including metabolic abnormalities, ectopic mucus production, urinary tract infections, stone formation, and even urological tumors [26,28].

In the past decade, tissue engineering has emerged as a transformative alternative to traditional surgical approaches for urinary system repair, which are limited by critical challenges [29–31]. Conventional methods relying on autologous tissues (e.g., intestinal segments for bladder reconstruction) or allografts are associated with

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significant complications, including immune rejection, morbidity at donor sites (e.g., infection, chronic pain, and bowel dysfunction), and shortage of healthy donor tissues. For instance, the use of intestinal grafts in bladder augmentation carries risks of metabolic imbalance and mucus secretion, while allogeneic transplants necessitate lifelong immunosuppression. These limitations have driven the development of tissue engineering strategies to regenerate functional urinary tissues. Recent advances in this field, such as biomaterial scaffolds (e.g., electroactive polymers and decellularized matrices) combined with stem cells or autologous micrografts, aim to bypass immune rejection by minimizing exogenous antigen exposure and eliminating donor site morbidity. Furthermore, engineered constructs can be tailored to match patient-specific anatomical requirements, addressing the scarcity of donor tissues. By recapitulating native tissue microenvironments through controlled scaffold design and cell integration, these approaches not only enhance regenerative capacity but also restore physiological function, ultimately improving long-term patient outcomes [32].

This review provides an overview of the current applications of tissue engineering in the urinary system. It further explores three key components of tissue engineering, detailing their functions and requirements. Additionally, it examines the needs and recent advancements in tissue engineering aimed at restoring biological function and organ classification. Finally, the review addresses the challenges encountered in the development of tissue engineering for the urinary system and offers future perspectives.

2. Tissue engineering technology

Tissue engineering (TE) is an interdisciplinary field that combines principles from biology, materials science, medicine, and engineering to develop innovative methods and therapies for tissue and organ regeneration [33]. It involves the repair of tissues using constructs made up of cells and scaffolds derived from the extracellular matrix (ECM) or synthetic materials, often supplemented with growth factors (Fig. 1) [34].

The core elements of tissue engineering—scaffolds, seed cells, and growth factors—synergistically enable functional tissue reconstruction. Scaffolds serve as 3D templates to mimic native extracellular microenvironments, while seed cells provide cellular sources for differentiation into target tissues. Growth factors orchestrate spatiotemporally specific signaling to regulate cell behaviors, regulating essential cellular behaviors such as proliferation, migration, and lineage commitment. Their dynamic interplay recapitulates developmental processes, guiding precise tissue repair and regeneration. This triad forms the foundation for translating tissue engineering strategies into clinical applications (see Table 1).

2.1. Scaffold materials

Scaffolds are a crucial component of tissue engineering and must possess a variety of essential properties. An effective scaffold should demonstrate excellent biocompatibility, cellular modifiability, mechanical strength, and appropriate degradability [35]. Based on the source of their raw materials, scaffolds can be classified into biological or synthetic categories [36,37]. However, biocompatible materials alone often lack sufficient mechanical properties. Therefore, in addition to promoting cellular potential, it is essential for these materials to exhibit strong mechanical characteristics. This combination enables the preparation of scaffolds that are both structurally and mechanically controllable, playing a vital role in tissue engineering [38,39].

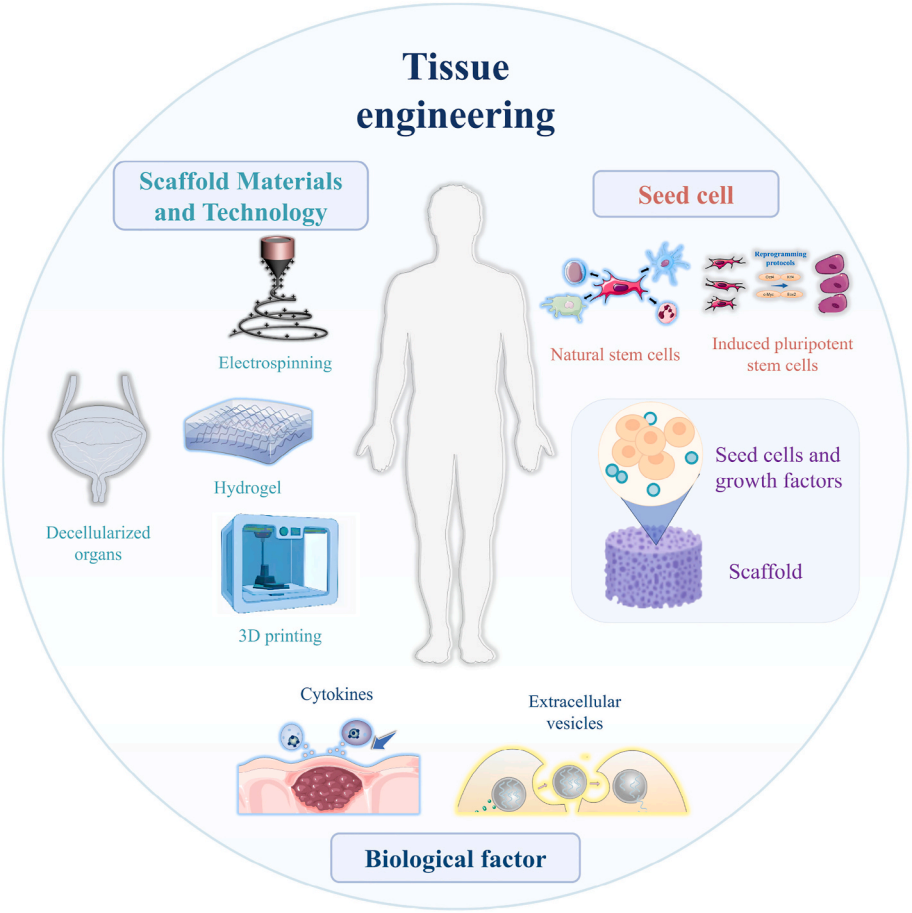

Fig. 1. Schematic representation of the three key elements of tissue engineering.

Table 1
Advancements in scaffold, seed cells, and biological factors for urinary system tissue engineering.

Scaffold Materials and Technology						
Component	Examples	Applications	Key Advantages	Current Challenges	Clinical Examples	Ref.
Natural Scaffolds	Collagen, Decellularized ECM (BAM, SIS), Amniotic Tissue	Bladder wall repair, Ureteral regeneration	High biocompatibility, Supports cell adhesion/ migration	Limited mechanical strength, Variability in decellularization protocols	BAM for porcine bladder repair	[1, 2]
Synthetic Scaffolds	PLGA, PCL, Electrospun PCL-laminin hybrids	Ureteral stents, Artificial tunica albuginea (ATA)	Tunable degradation, High mechanical strength	Lack of bioactive signals, Risk of encrustation	Biodegradable ureteral stents (PLGA)	[3, 4]
Hybrid Scaffolds	PEDOT-POCO composites, Strain-hardening hydrogels (ATA)	Bladder regeneration, Dynamic tissue repair	Electroactivity, Adaptive mechanical properties	Complex fabrication, Scalability challenges	PEDOT-POCO in porcine cystectomy models	[5, 6]
Fabrication Technologies	3D bioprinting, Electrospinning, Layer-by-Layer (LbL) systems	Complex defect repair, Smart drug delivery	Spatial control, Dynamic responsiveness	Regulatory hurdles, High cost of GMP compliance	3D-printed urethral scaffolds in canine models	[7, 8]
Seed Cells						
Component	Examples	Applications	Key Advantages	Current Challenges	Clinical Examples	Ref.
Autologous Cells	Urinary-derived stem cells (USCs), Smooth muscle cells (SMCs)	Urethral reconstruction, Bladder repair	Low immunogenicity, Patient-specific	Carcinogenesis risk in cancer patients, Pathological cell limitations	USC-seeded scaffolds in preclinical models	[9–11]
Stem Cells	MSCs, hiPSCs (small-molecule reprogrammed)	Chronic kidney disease, Bladder regeneration	Multidirectional differentiation, Paracrine effects	Genetic instability (hiPSCs), Aging in culture	MUVON SUI Phase II trial	[12–14]
Cell-Free Strategies	Cell sheet technology (CST), MSC-derived exosomes	Skin/cornea repair, Acute kidney injury	No scaffold rejection, Preserved cell-surface proteins	Long preparation time (CST), Exosome mechanism unclear	Exosome therapy in murine AKI models	[15–18]
Biological Factors						
Component	Examples	Applications	Key Advantages	Current Challenges	Clinical Examples	Ref.
Growth Factors	VEGF, TGF-β, FGF-2	Vascularization, ECM remodeling	Enhances tissue integration, Reduces fibrosis	Short half-life, Off-target effects	VEGF-eluting hydrogels in diabetic wounds (VASCON trial)	[19–21]
Exosomes	MSC-derived exosomes (miRNA, cytokines)	Anti-apoptosis, Pro-angiogenesis	Carries bioactive signals, Low immunogenicity	Unclear mechanism, Scalable production challenges	Exosomes in murine acute kidney injury	[22]
Other Bioactive Molecules	Cytokines (e.g., IL-10), Nitric oxide	Inflammation modulation, Urethral regeneration	Targeted signaling, Synergistic effects	Stability during delivery, Dose optimization	Nitric oxide-coated stents in preclinical models	[23–25]

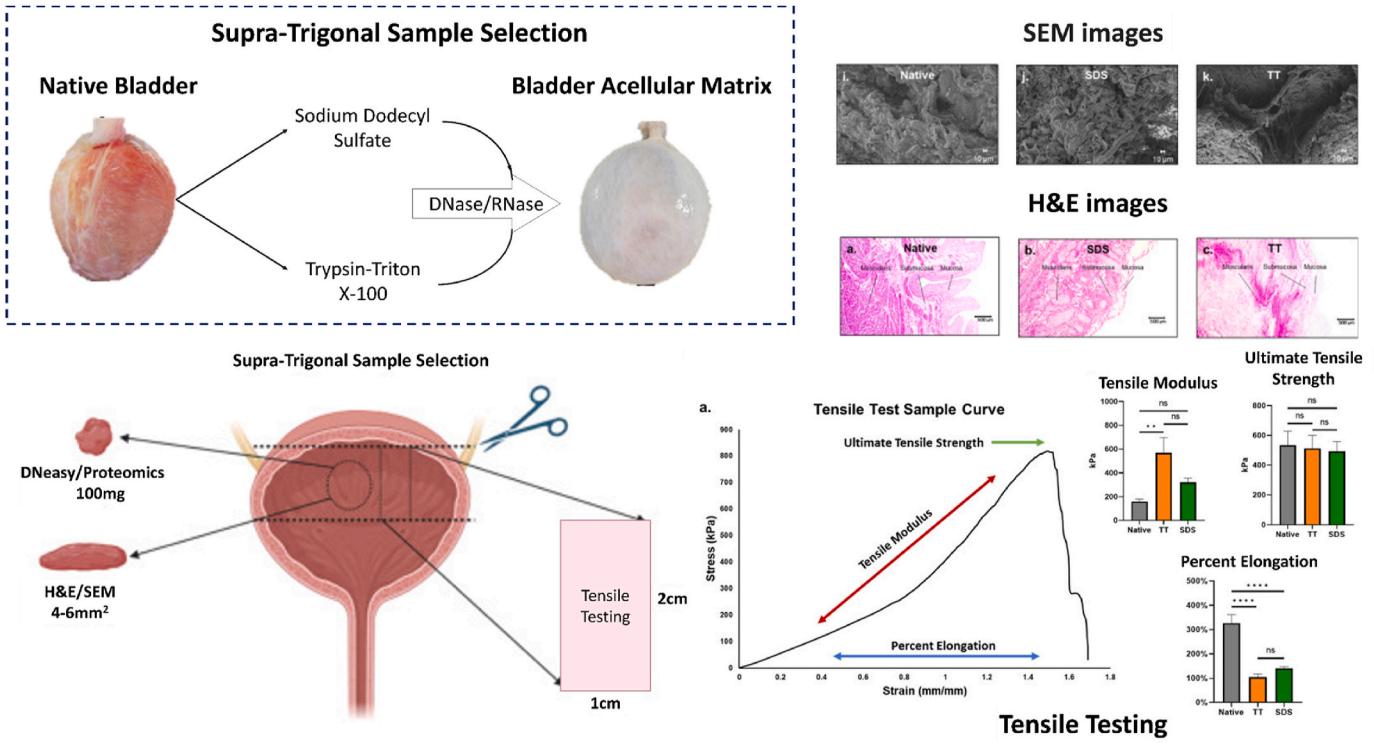

Fig. 2. Schematic illustrating two methods of bladder decellularization, with subsequent H&E staining, SEM, and tensile testing. The results show that both methods exhibit good porosity and mechanical properties. Reproduced with permission [44]. Copyright Elsevier.

Materials for natural-source scaffolds include collagen, glycosaminoglycans, and fibroin. Decellularized matrix scaffolds are typically derived from tissues such as bladder acellular matrix (BAM) [1,2], small intestinal submucosa (SIS) [40], gallbladder [41,42], and amniotic tissue [43]. Scaffolds derived from natural materials exhibit favorable biological properties, degradability, and a robust 3D structure.

Decellularized substrates have been used in surgical applications, biological dressings, and tissue engineering for an extended period. However, their effectiveness has often shown variability, with a significant factor contributing to these differences being the selection of decellularization protocols. Despite this, few studies systematically compare the efficacy of these protocols in preserving mechanical properties and protein content. In this study, two distinct detergent and enzyme treatment regimens were employed to characterize bladder acellular matrix, focusing on their effects on nucleic acid and DNA removal (≥90 %), structural integrity, tensile properties, and maintenance of extracellular matrix proteins. Porcine bladder tissue was subjected to decellularization using a stirring regimen involving either 0.5 % sodium dodecyl sulfate (SDS) or 0.25 % trypsin-Triton X-100 hyperosmolar (TT), followed by DNase/RNase treatment. The resulting matrices were assessed through histological analysis, scanning electron microscopy (SEM), and tensile testing. Post-decellularization results showed that the tensile modulus of the TT group increased, while its extensibility decreased. However, both protocols did not significantly affect the ultimate tensile strength (UTS) (Fig. 2). Decellularization enhanced deformation resistance in scaffolds from both groups. Future research into the application of biological scaffolds must consider the treatment methods and reagents used to ensure that selected materials optimize desired properties while promoting effective translational applications [44].

The materials commonly used for synthesizing scaffolds include polylactic acid (PLA), polyglycolic acid (PGA), and poly(lactic-co-glycolic acid) (PLGA) [3]. These materials offer several advantages, including non-toxicity, high mechanical strength, a certain degree of degradability, and ease of processing for modification.

Hydrogels, as widely used medical biomaterials, are employed in various disciplines, including tissue engineering. In this field, hydrogel scaffolds are favored for their ability to form porous structures that are both structurally and mechanically compatible with the target organ. These scaffolds provide a favorable microenvironment that supports cell growth, adhesion, and migration [45,5]. One of the key advantages of hydrogels is their ability to prevent the formation of fibrous tissue induced by hypoxia or ischemia, a common challenge in tissue engineering. This property facilitates more effective tissue repair, ultimately aiding in the restoration of normal tissue function.

The white membrane in mammals features a double-layer orthogonal structure composed of stacked, parallel, wavy collagen fibers. During the process of erection, these fibers gradually straighten and elongate, facilitating the transition from a soft to a hard state. Inspired by the highly adaptive strain structure of natural white membranes, Chai et al. proposed an artificial white film (ATA) (Fig. 3), created through strain-hardening hydrogel composed of aligned, crimped fibers. This complex structure is achieved by stretching an isotropic polyvinyl alcohol (PVA) gel, followed by covalent cross-linking. Similar to its natural counterpart, ATA exhibits rapid strain hardening, exceptional fatigue resistance, and high toughness within small deformation ranges [6].

Electrostatic spinning (ESP) is a versatile and adjustable textile technology used to produce tubular materials. This process involves either directly collecting micro- and nano-fibers onto rotating receiver rollers or winding micro- and nano-fiber membranes around mandrels. ESP allows for the regulation of fiber surface structure and the aggregate structure of fibers at three distinct scales: fiber, yarn, and fabric. This capability enables the technology to closely mimic the extracellular matrix, promoting cell growth and tissue regeneration. As a result, ESP is widely employed in biomedical and related fields [7,8].

Electrospinning of polymers has become a widely used method for preparing fiber scaffolds in tissue engineering due to its ability to easily manipulate both the structure and chemistry of the materials. However, scaffolds made from synthetic polymers often lack the natural biomolecular signals that are crucial for cellular function. These signals can be introduced by incorporating bioactive agents, such as proteins, into the polymer matrix. In this study, scaffolds were fabricated using an electrospinning platform, with laminin added to a polycaprolactone (PCL) solution through two methods: direct mixing and emulsion electrospinning (Fig. 4). SEM was employed to examine the scaffold structure and cell morphology, assess the mechanical properties of the scaffolds, and evaluate cell adhesion and survival. SEM images revealed that the electrospun scaffolds had similar structures, with the smallest fiber diameters observed in the emulsion group. Cell experiments demonstrated

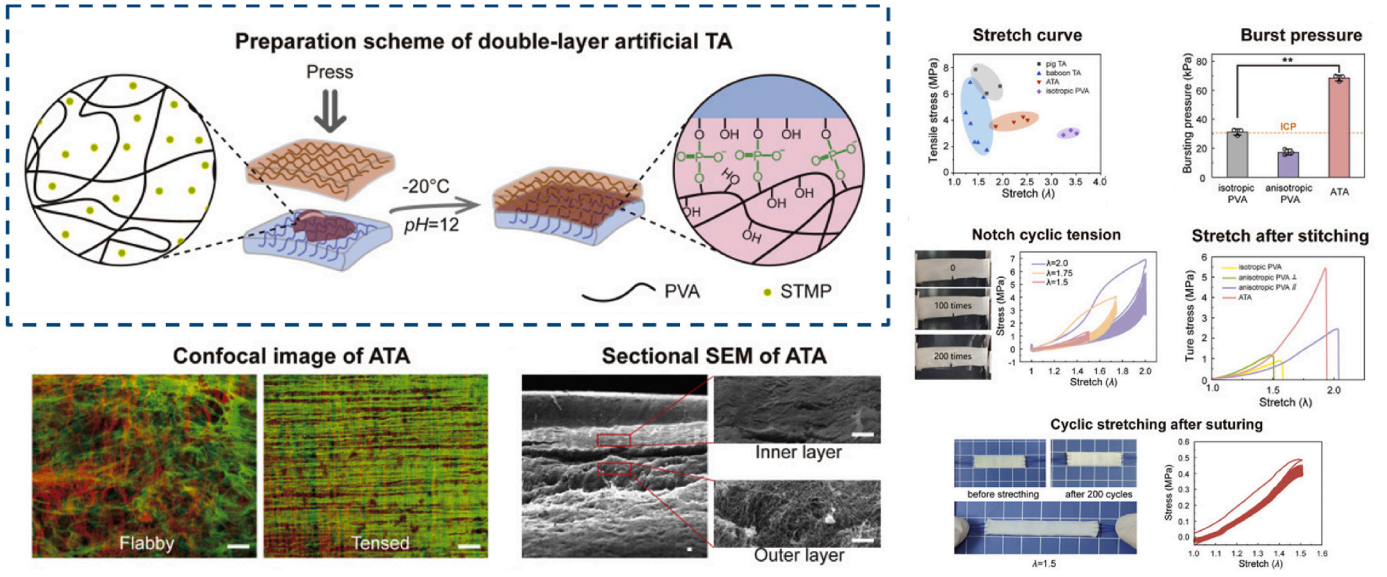

Fig. 3. Method of preparation, confocal and scanning electron microscope photos of the hydrogel artificial white film (ATA). The mechanical properties test demonstrated that the material exhibited superior mechanical characteristics when compared to both natural materials and PVA. Reproduced with permission [6]. Copyright Elsevier.

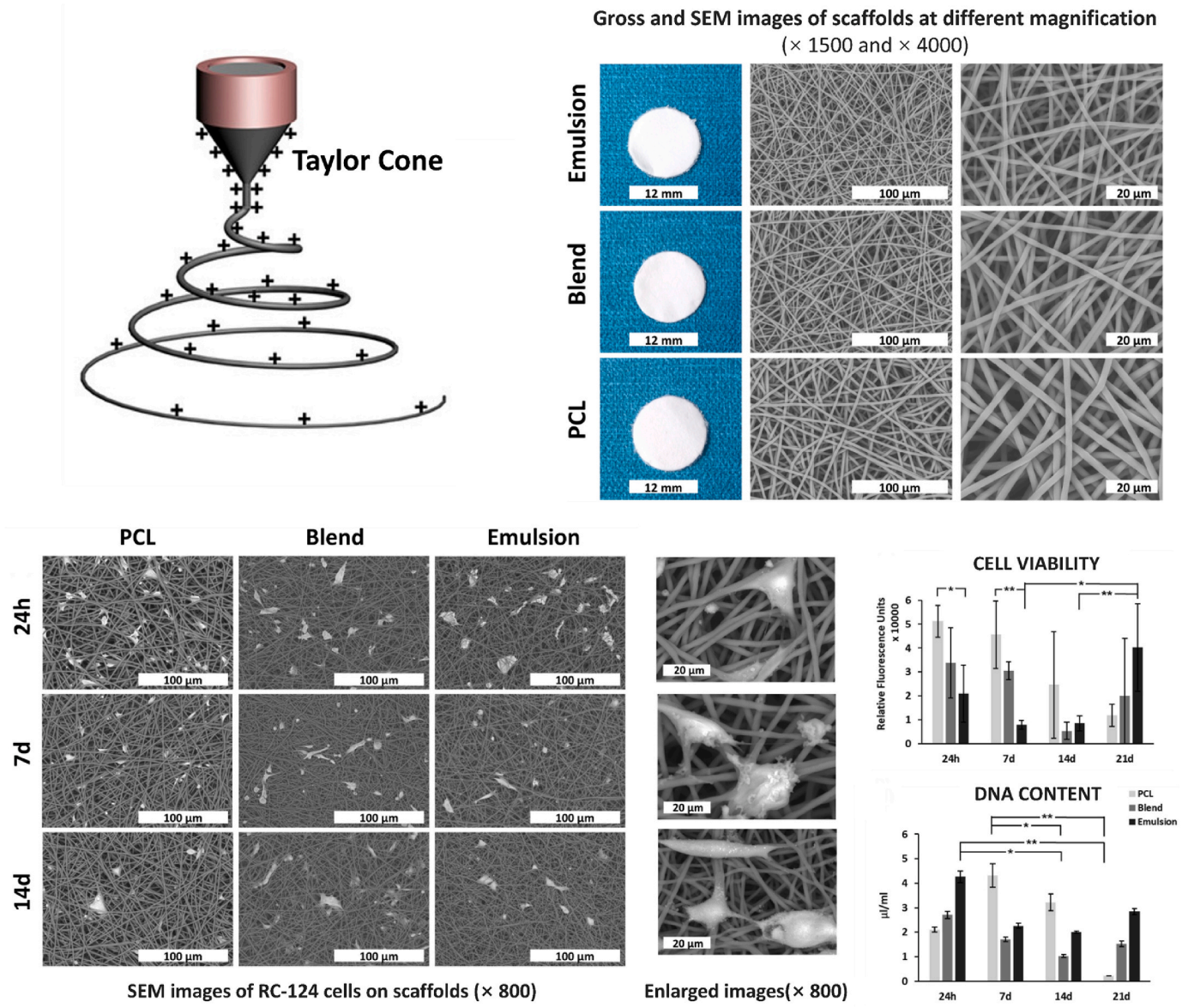

Fig. 4. Gross imaging and SEM of electrospun materials prepared in three different proportions, SEM analysis of cell-cell and cell-fiber interactions, and cell viability and DNA content experiments at different time points. The results showed that the addition of adhesion protein in the middle layer of electrospinning can change the mechanical properties of the polymer, enhance the elasticity, show good biocompatibility , and promote gene expression. Reproduced with permission [4]. Copyright 2019 ACS Publications.

that kidney cells could adhere to and survive on the electrospun fibers for up to three weeks. Gene expression analysis indicated that laminin supplementation helped maintain cell health. The results showed that the incorporation of laminin altered the mechanical properties of the polymer, enhancing its elasticity, and the scaffold exhibited excellent biocompatibility and the ability to promote gene expression. These findings underscore the importance of further investigation into the combination of extracellular matrix (ECM) proteins and synthetic polymers for renal tissue engineering applications [4].

Cell sheet technology (CST) is primarily utilized in the field of tissue engineering for repair and holds promising clinical application prospects [15,16]. In recent years, techniques such as plasmid transfection and gene editing have been employed to modify cells, enabling their cultivation into cell sheets that enhance factor secretion or enable the secretion of new cytokines. This has further expanded the therapeutic capabilities of cell sheets [17,18]. In clinical applications, membranes derived from stem cells, epithelial cells, and cardiomyocytes have shown satisfactory efficacy in repair tests for skin, cornea, middle ear mucosa, and myocardium, leading to their practical application [46,47]. More recently, a study has developed bladder cancer cell membrane patches, providing valuable tools for both in vivo and in vitro research on bladder cancer, as well as for personalized drug selection in patients [48].

CST is a scaffoldless tissue engineering technique that primarily involves obtaining tightly connected living cell tissue slices and an autocrine extracellular matrix by adjusting the temperature of the cell culture. This method preserves key proteins on the cell surface, such as ion channels, growth factor receptors, and intercellular junctions. As CST does not require external scaffold materials, it avoids issues related to rejection and ethical concerns, while also addressing the shortage of available repair materials.

In this study, a small quantity of oral and adipose tissue was collected to isolate adipose-derived stem cells (ADSCs), oral mucosal epithelial cells, and oral mucosal fibroblasts for the preparation of cell tablets. Hematoxylin and eosin (HE) staining revealed that the average thicknesses of the oral mucosal epithelial cell tablet, oral fibroblast tablet, and ADSC myoblast induction tablet were approximately 25 μm, 60 μm,

and 90 μm, respectively. SEM revealed the characteristic pebble-like morphology of the oral epithelial cells. The oral fibroblasts exhibited a uniformly flat appearance with abundant fibrous cords, while the ADSC tablets induced with myoblasts displayed tight cellular connections arranged in a striped pattern. Immunohistochemical analysis showed positive staining for vimentin and pan-cytokeratin (AE1+AE3) in both the oral fibroblast and oral mucosal epithelial cell tablets, confirming their origins from fibrous connective tissue and epithelium, respectively. Furthermore, after three weeks of culture in myoblast differentiation medium, myoblasts derived from ADSC sheets showed positive expression of α-SMA, desmin, and PAX7 markers, which are indicative of muscle cell differentiation (Fig. 5) [49].

However, the clinical application of cell membranes still faces the challenge of balancing the long culture cycle required for membrane preparation with the timing constraints of elective surgeries. Additionally, industrialization issues must be addressed. A key research direction will be finding effective methods to preserve mature cell membranes and make them readily available on demand. In the design of tissue-engineered ureteral stents, the structure of natural ureteral tissue should be carefully considered, particularly the orientation of the inner and lateral muscle layers of smooth muscle tissue. Developing structural designs that can replicate these natural tissue features for the reconstruction of the ureter remains an area for further study.

The application of multifunctional biomaterials plays a vital role in the structural and functional reconstruction of stents for urinary tissue engineering. These materials enhance both the mechanical support and the regeneration of damaged tissues by mimicking the physiological behavior of the urinary tract. Emerging technologies, such as 3D bioprinting, offer precise control over cell-laden biomaterials, allowing for the creation of complex, tissue-like structures that promote tissue regeneration in the urinary system. Layer-by-layer (LbL) technology, based on electrostatic attraction, enables the creation of multi-layered scaffolds with fine control over their composition and structure. This approach enhances the bioactivity of the scaffolds by incorporating functional molecules and improving cell interaction, which is crucial for successful tissue repair.

Looking ahead, the design of urologic tissue-engineering stents will increasingly focus on molecular and bionic approaches. These strategies aim to more accurately replicate the natural architecture and function of urinary tissues, enhancing the regeneration and long-term integration of stents. Future innovations may resolve the biocompatibility-mechanical strength trade-off through the development of dynamic biomaterials that adapt stiffness in response to microenvironmental cues (e.g., enzymatic activity or pH shifts), or through hierarchical composites mimicking the elastin-collagen synergy in native urinary tracts. Additionally, integrating machine learning-driven biomaterial design with high-throughput mechanical testing could accelerate the discovery of hybrid systems that optimize and balance both bioactivity and load-bearing requirements.

2.2. Seed cells

Compounding seeded cells onto scaffolds has been shown to promote tissue regeneration and enhance tissue-engineered repair [50–53]. Seeded scaffolds provide better tissue integration and urodynamic outcomes compared to non-seeded scaffolds, potentially preventing fibrosis. In bladder tissue engineering, the use of seeded cells on scaffolds has been demonstrated to effectively prevent tissue fibrosis [53].

Autologous cells used in urinary tissue engineering primarily include urinary-derived stem cells (USCs) and smooth muscle cells (SMCs). In theory, autologous cells are the optimal choice for tissue repair due to their ability to reduce immune rejection following implantation. However, their use is limited. For instance, there is a risk of carcinogenesis when autologous cells are used in tumor patients [54,9]. Additionally, when smooth muscle cells are employed for bladder repair in cases of neuronal dysfunction, pathological changes such as increased cell proliferation, decreased adhesion, and reduced contraction have been observed [10]. Furthermore, abnormal cells obtained from damaged tissues are not suitable for reconstructing new tissues in patients with congenital disorders, infections, or radiation exposure [11].

Stem cells, including bone marrow mesenchymal stem cells (MSCs) and urinary-derived stem cells (USCs), exhibit substantial potential in bladder tissue engineering applications due to their capacity for self-renewal and multidirectional differentiation, coupled with their low immunogenicity. MSCs are pluripotent stem cells that can be isolated from various tissues, such as bone marrow, adipose tissue, peripheral blood, umbilical cord blood, and liver. These cells have the potential to proliferate and differentiate into a variety of cell types both in vitro and in vivo [9]. MSCs can differentiate into smooth muscle cells, thereby aiding bladder repair and promoting angiogenesis and neurogenesis through paracrine signaling [12,13]. In recent years, significant advancements have been made in the application of human induced

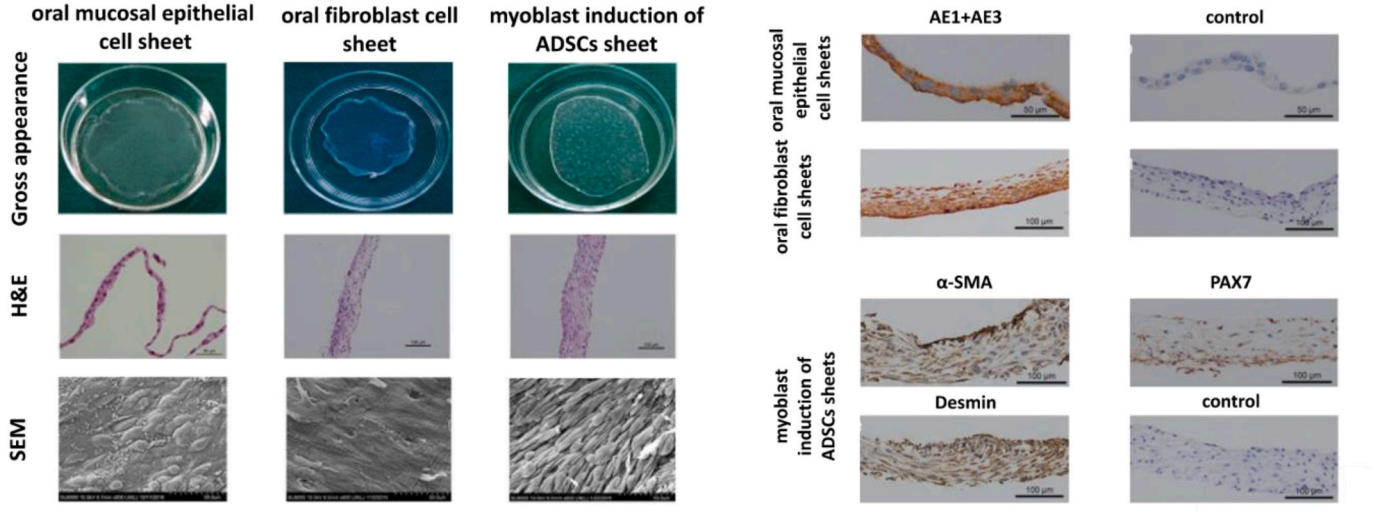

Fig. 5. Overall morphology, H&E staining, SEM, and immunohistochemical analysis of cell sheets derived from three distinct cell types. The results illustrate that the oral fibroblast cell sheet and oral mucosal epithelial cell sheet showed fibrous connective tissue and epithelium, and the myoblast induction of ADSCs cell sheet showed myocyte differentiation. Reproduced with permission [49]. Copyright Ivyspring International Publisher.

pluripotent stem cells (hiPSCs) in organ and tissue engineering, demonstrating considerable potential for treating chronic kidney disease. Furthermore, mesenchymal stem cells (MSCs) have proven beneficial in the treatment of chronic kidney disease [14].

HiPSCs exhibit substantial potential in cell therapy and tissue engineering applications. These cells are somatic cells reprogrammed into pluripotent stem cells through the introduction of specific transcription factors. They exhibit similar morphology and biological properties to embryonic stem cells, rendering them a valuable source of patient-specific stem cells for regenerative medicine applications [55].

HiPSCs, generated by reprogramming somatic cells using transcription factors, offer patient-specific therapeutic potential for regenerative medicine while circumventing ethical concerns associated with embryonic stem cells. However, genetic instability during reprogramming poses oncogenic risks, exacerbated by factors such as oxidative stress, genomic aberrations, and residual expression of oncogenic transcription factors like c-Myc/Klf4 activity [55]. To address these concerns, recent advancements in small-molecule reprogramming, non-integrative delivery systems, and stringent genomic screening protocols have been explored to enhance the safety of hiPSC-derived therapies for clinical applications. Small molecules are increasingly used to replace traditional Yamanaka factors (Oct4/Sox2/Klf4/c-Myc), thereby eliminating risks from viral integration and oncogene reactivation [56]. For example, Hou et al. demonstrated that a chemical cocktail (VPA + CHIR99021) achieved 0.2 % reprogramming efficiency in fibroblasts without genomic integration, while reducing teratoma formation by 70 % compared to viral methods [57]. Non-viral delivery systems, including episomal vectors, mRNA transfection, and protein-based methods, avoid permanent genetic modifications. Additionally, rigorous characterization protocols now mandate whole-genome sequencing (WGS) to detect structural variants, karyotyping for chromosomal stability, and epigenetic profiling to assess imprinting errors. The European iPSC Bank initiative has established benchmarks requiring <5 % aneuploidy and zero detectable oncogenic mutations for clinical-grade lines.

However, the research and application of adult stem cells face several challenges. These cells are prone to aging in culture, and their capacity to repair and regenerate damaged tissues gradually diminishes. Additionally, the number of stem cells in adult tissues is very low, making the isolation of high-purity, high-quality adult stem cells a significant challenge. Furthermore, when adult stem cells are isolated from diseased tissues or from patients with genetic disorders, genetic modification may be necessary before they can be used clinically [58].

Recently, non-cellular scaffolds loaded with cytokines have been proposed to promote cell recruitment and enhance tissue repair (Fig. 6). This approach offers good biosafety, as the recruited cells are autologous. However, inducing cell differentiation during this process remains a critical consideration. Efforts are currently underway to selectively capture autologous cells for disease diagnosis and treatment by cross-linking microchips, scaffolds, and/or platforms with specific antibodies [23–25]. This strategy has shown promise as a tissue repair technique.

Seed cells play a crucial role in urethral regeneration by acting as a mechanical barrier against the invasion of bladder lining. Additionally, exosomes and specific molecules, such as nitric oxide and human beta-defensin, secreted by seed cells promote local regeneration of injured urethral tissue. However, the use of seed cells carries several risks, including carcinogenesis and genomic instability or mutations. Reprogramming-related gene mutations (e.g., c-Myc, Sox2, Oct4, and Klf4) are also significant concerns during the regeneration process. To manage these risks, potential strategies include the use of primitive pluripotent cells, specially designed tissue engineering scaffolds (TFS), continuous imaging monitoring techniques, and exosome extraction (Fig. 7) [59].

In tissue engineering, the combination of seed cells and specially designed scaffolds creates a supportive microenvironment that is critical for successful urethral regeneration. Key biological processes such as vascularization and fibrosis play essential roles in tissue repair and integration, ensuring the development of functional tissue. The advancement of cutting-edge techniques, including genetic engineering, molecular imaging, and exosome extraction, has greatly improved the management of regeneration-related risks associated with seed cells. These innovations enhance the behavior of seed cells, minimizing adverse effects such as inflammation or aberrant tissue growth. By optimizing cell survival, differentiation, and integration, these methods significantly improve the safety and efficacy of regenerative therapies, making them more viable for clinical application in urethral tissue engineering.

2.3. *Bioactive molecules: growth factors, cytokines, and beyond*

Growth factors are peptides that facilitate intercellular communication and regulate cell growth, proliferation, and differentiation [19,20]. Growth factors are extensively utilized in tissue engineering, including platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), insulin-like growth factor (IGF), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), and so on. Their primary functions involve the regulation of cellular activities, the promotion of angiogenesis, and the induction of tissue regeneration [21]. In addition, the role of certain novel bioactive substances cannot be overlooked. Exosomes, as the primary active substance in the paracrine effect of stem cells. They are released into the extracellular matrix after the fusion of intracellular multivesicular bodies and the cell membrane. Specifically, exosomes now refer to disc-shaped vesicles with a diameter

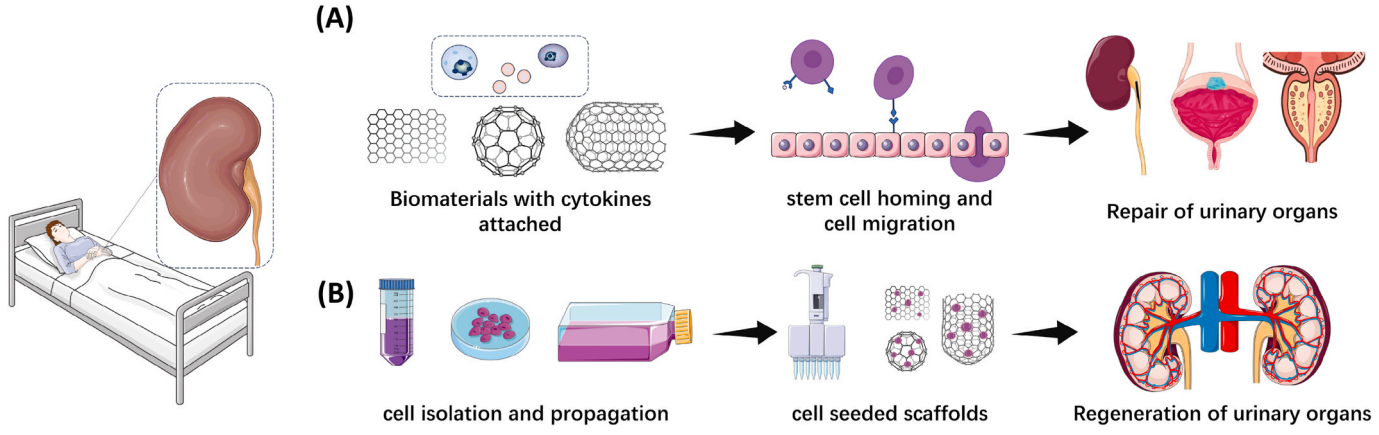

Fig. 6. Tissue engineering strategies for bladder replacement include non-cellular grafts (A) and cellular grafts (B).

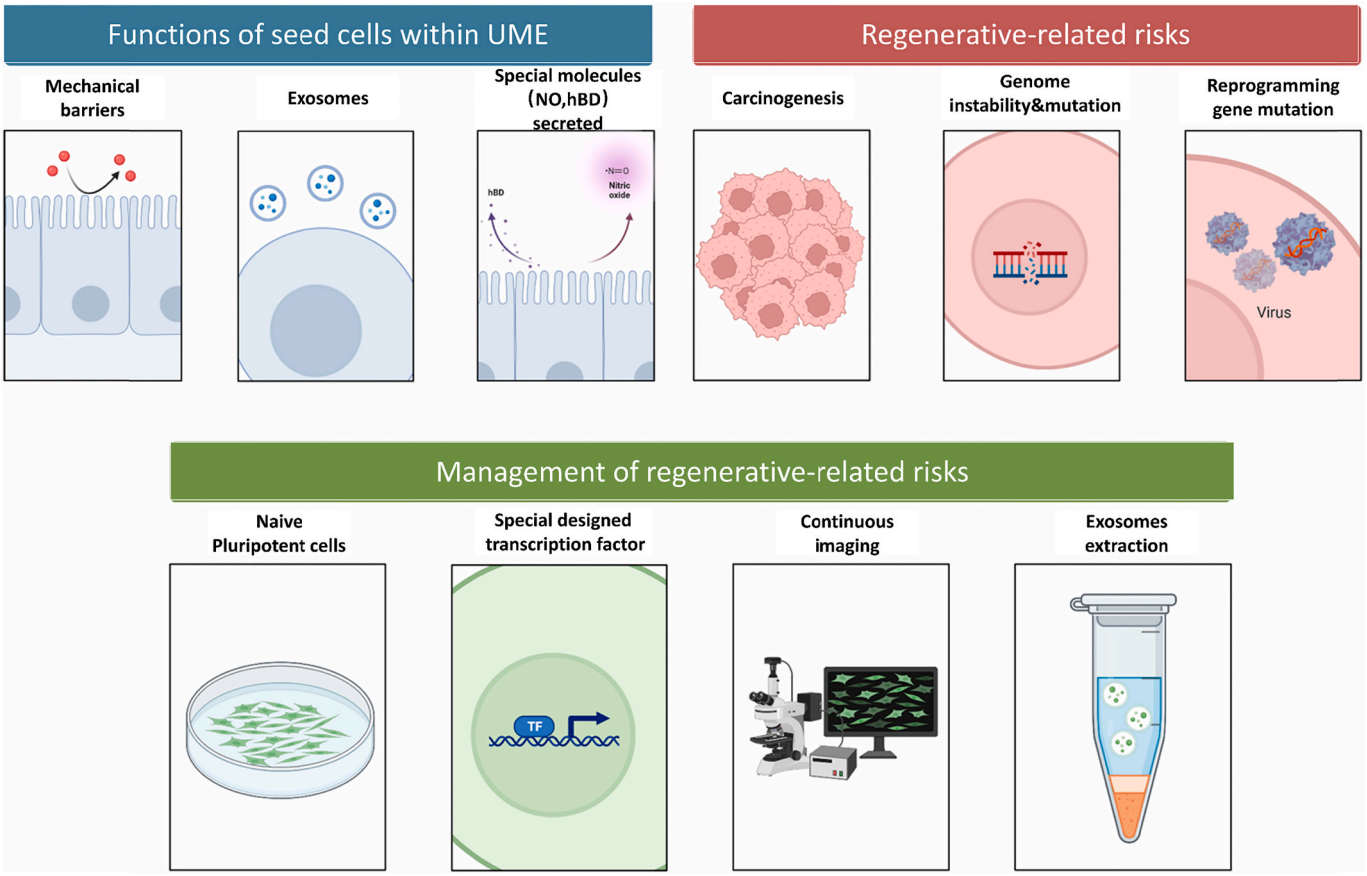

Fig. 7. Functions, risks, and management strategies related to seed cells. Reproduced with permission [59]. Copyright Springer Nature.

of 30–100 nm, carrying biological information from their corresponding cell of origin.

Exosomes derived from mesenchymal stem cells (MSCs) contain a diverse range of proteins, lipids, and both coding and non-coding RNA. Additionally, they transport cytokines and growth factors that are essential for promoting cell proliferation and inhibiting apoptosis (Fig. 8). In an in vitro assay, Collino et al. demonstrated that exosomes derived from bone marrow MSCs could prevent apoptosis in renal tubular epithelial cells and stimulate their proliferation. Furthermore, these exosomes significantly improved renal morphology and function in a mouse model of glycerol-induced acute kidney injury [22].

Further research into the function and mechanisms of exosomes, as well as other bioactive molecules, will provide new insights into their roles in tissue regeneration and repair. These molecules carry bioactive signals, including proteins, lipids, and RNA, that influence cellular behavior, such as differentiation, proliferation, and extracellular matrix remodeling. Understanding the detailed mechanisms through which exosomes and cytokines exert their effects will establish a solid theoretical foundation for their potential therapeutic application in treating urinary tract injuries and other tissue damage. As research progresses, it is expected that a wider array of bioactive substances, including growth factors and other signaling molecules, will be identified and characterized. These substances are crucial for orchestrating the complex biological processes of tissue regeneration, such as angiogenesis, inflammation resolution, and tissue remodeling. Advancements in the delivery systems and formulation strategies for these factors will allow for greater control over their release profiles, enhancing the efficacy and specificity of treatments. The research is progressing toward improving the efficiency, accuracy, and controllability of biological factors to achieve more precise modulation of the regenerative environment. By refining these factors and their delivery mechanisms, the clinical translation of tissue engineering technologies can be accelerated, paving the way for their widespread implementation in regenerative medicine. This will help to develop more effective therapies for a variety of tissue injuries, including urinary tract injuries, and improve the outcomes of tissue engineering interventions.

The efficient delivery and precise spatiotemporal regulation of cytokines remain pivotal challenges in tissue repair and regenerative medicine. Spatiotemporally controlled release systems enable precise therapeutic modulation through advanced carrier design: polymeric microspheres achieve sustained cytokine release by programming polymer degradation kinetics, extending local bioavailability, while photothermal response platforms allow on-demand payload release via external triggers, reducing off-target effects. Synergistic delivery strategies further enhance therapeutic efficacy through coordinated multifactor actions. For example, VEGF/bFGF co-delivery significantly improves vascularization efficiency by sequentially targeting endothelial cell proliferation and vascular maturation. Hydrogel- or nanoparticle-mediated co-delivery systems demonstrate spatiotemporal synchronization of dual-factor release, addressing the limitations of single-factor therapies [60]. Current research focuses on intelligent delivery systems integrating spatiotemporal control with combinatorial delivery approaches to advance complex tissue regeneration paradigms.

The tissue regeneration microenvironment is shaped by interactions among seed cells, scaffolds, regenerative factors, and host tissue. These components dynamically collaborate to drive healing and functional restoration. Understanding their synergistic mechanisms is essential for revealing molecular pathways and developing therapeutic strategies that mimic natural healing. Elucidating these interactions enables precise tissue engineering approaches, advancing novel treatments for regenerative barriers.

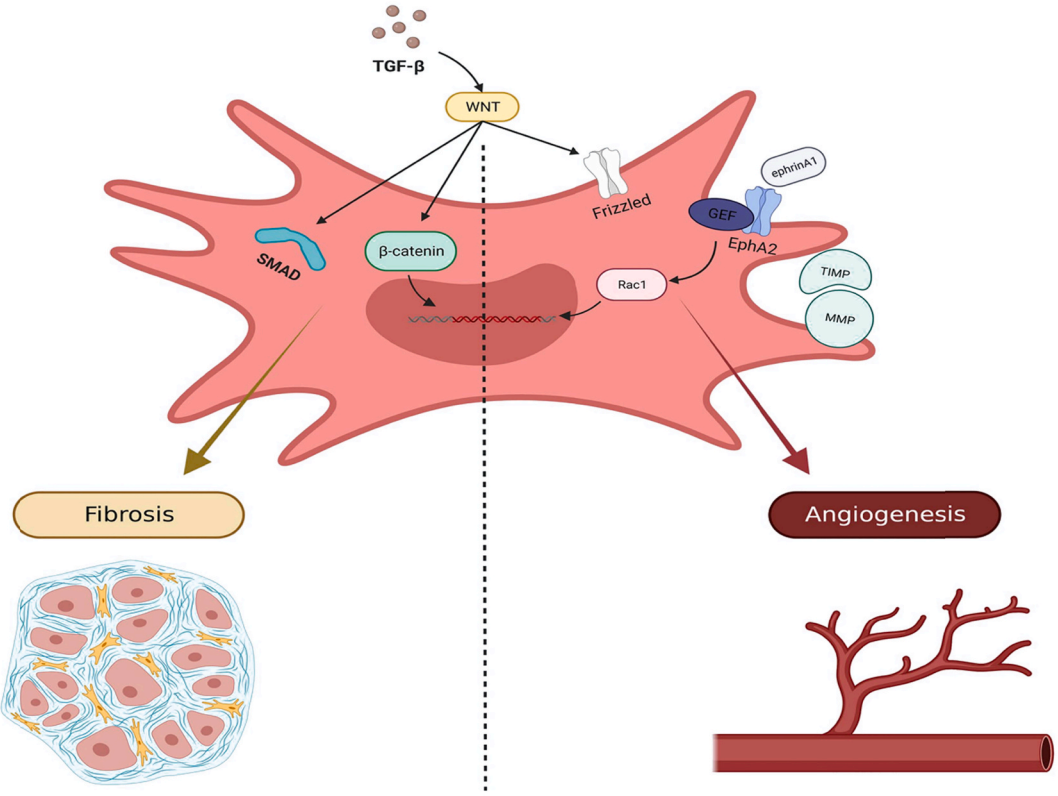

Fig. 8. Schematic diagram of the TGF-β/Wnt and ephrinA1/EphA2-GEF/Rac1 signaling pathways. Reproduced with permission [59]. Copyright Springer Nature.

3. Biology of urinary system

Moderate mechanical properties of biological scaffold materials are essential to address post-implantation challenges, such as urine pressure [61]. Furthermore, these materials must possess additional functional properties to promote tissue repair and enhance their structure and function, allowing them to better mimic normal tissue (Fig. 9) [62,63].

3.1. Epithelialization

The urinary tract is continually exposed to a complex biochemical and biodynamic environment [64]. Regardless of whether the bladder is empty or in various stages of filling, both the layers and morphology of the epithelium undergo alterations to prevent urinary erosion (Fig. 10). Following pathological injury caused by bacterial infection or chemical damage, the basal cells of the urinary epithelium proliferate rapidly, facilitating the complete regeneration of the epithelium [65]. Therefore, achieving successful epithelial regeneration in the urinary tract is crucial for advancing tissue engineering in urology, particularly for the restoration of bladder function and the treatment of various urological disorders. By overcoming the challenges related to epithelialization, tissue engineering strategies will become increasingly effective in restoring normal urinary tract function and improving patient outcomes [32].

3.2. Vascularization

The formation of blood vessels is a critical goal in tissue engineering for regenerative medicine [66]. While some thin tissues, such as the cornea, epidermis, and cartilage, rely on nutrients and oxygen diffusing from capillaries, most tissues require direct proximity to blood vessels to supply adequate nutrients and oxygen [67,68]. In vivo implantation of tissue-engineered grafts can only deliver oxygen and nutrients to a depth of 200 μm without vascularization. If spontaneous vascularization occurs post-implantation, the inward growth of blood vessels is often

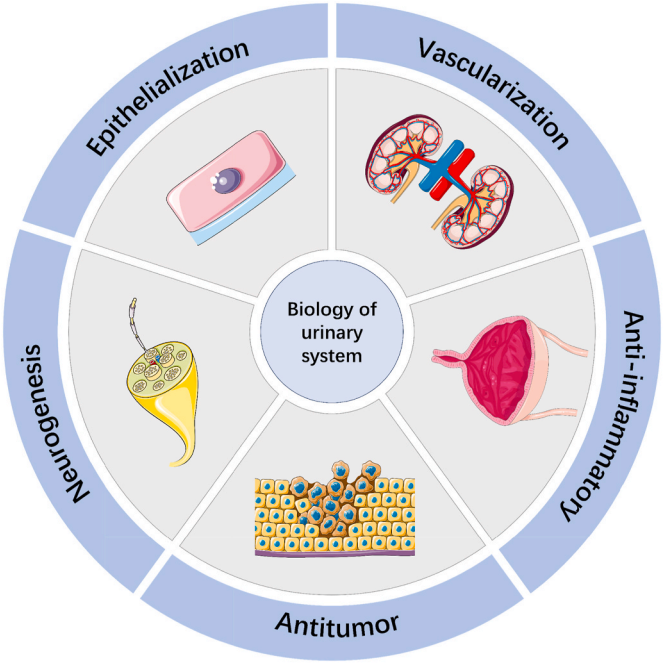

Fig. 9. Diagram of the functions required for tissue engineering repair of the urinary system.

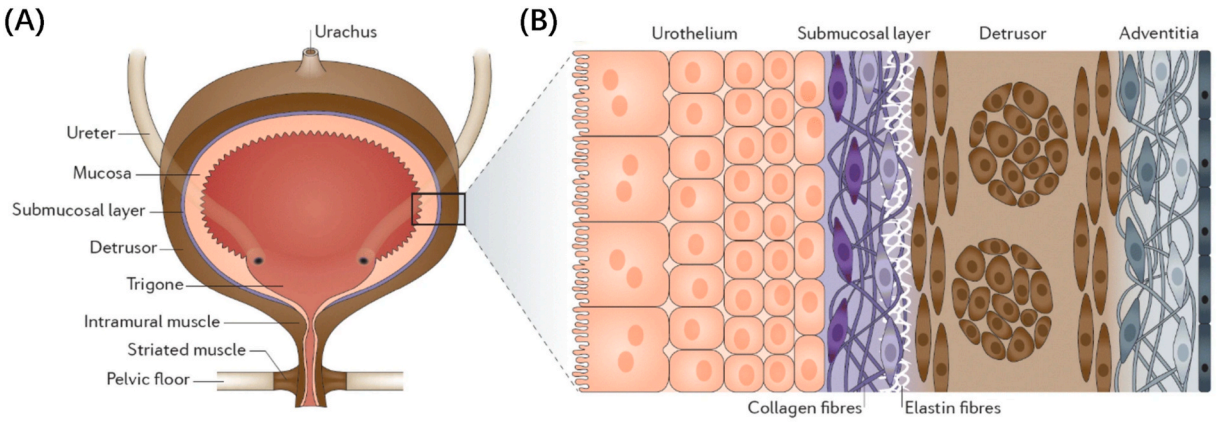

Fig. 10. Structural anatomy and histological features of the bladder. (A) The four-layered structure of the bladder wall, consisting of the mucosal layer (uroepithelium), submucosal connective tissue layer (lamina propria), muscularis propria, and plasma membrane layer. (B) The multilayered uroepithelium, comprising basal, intermediate, and umbrella cells, which form a blood- and urine-permeable barrier against urinary erosion. Reproduced with permission [62]. Copyright Springer Nature.

insufficient, leading to cell death in the core due to nutrient deprivation and hypoxia [69]. Thus, a functional vascular network capable of transporting oxygen and nutrients is essential for successful tissue regeneration after implantation [66,69].

Although biomaterials can partially form blood vessels spontaneously after implantation, these vessels are typically inadequate for therapeutic applications [70]. The formation of blood vessels can be enhanced by the addition of pro-angiogenic factors such as vascular endothelial growth factor (VEGF), matrix metalloproteinases (MMP), basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), angiotensin (Ang), and hepatocyte growth factor (HGF). Therefore, carefully optimizing the release mechanisms and the delivery of these pro-angiogenic factors is essential to ensure effective vascularization and support the long-term success of tissue-engineered constructs.

In a recent study, Zhao et al. developed an artificial decellularized nanocomposite scaffold (ANS), incorporating stromal vascular fraction (SVF) secretome loaded onto imidazolate framework-8 (ZIF-8) nanoparticles. This ANS was then combined with a bladder decellularized matrix, promoting gradient degradation and controlled release of SVF secretome to stimulate tissue regeneration. Flow cytometry analysis revealed that the SVF consists of a heterogeneous population expressing markers characteristic of hematopoietic stem cells (Fig. 11A). When diluted in DMEM, these cells were inoculated into a 3.5 cm petri dish at a final concentration of 1000 cells per plate, confirming the clonogenic potential of SVF cells (Fig. 11B). Moreover, angiogenesis assays demonstrated that SVF cells can form capillary-like structures within Matrigel (Fig. 11C) [71].

Vascularization remains one of the most significant challenges in tissue engineering, particularly when it comes to the creation of large tissue constructs that can effectively integrate with the host vasculature. However, the limited applicability of current strategies in overcoming this issue has been primarily attributed to their reduced vascularization capacity, which hinders the efficient delivery of oxygen and nutrients to the center of engineered tissues, leading to poor tissue viability and function [72]. To improve this limitation, pre-vascularization of tissue structures—defined as the creation of well-structured capillary networks within engineered tissues prior to transplantation—has been explored as a promising approach to enhance vascular integration. This strategy aims to ensure that the tissue grafts are more likely to integrate with the

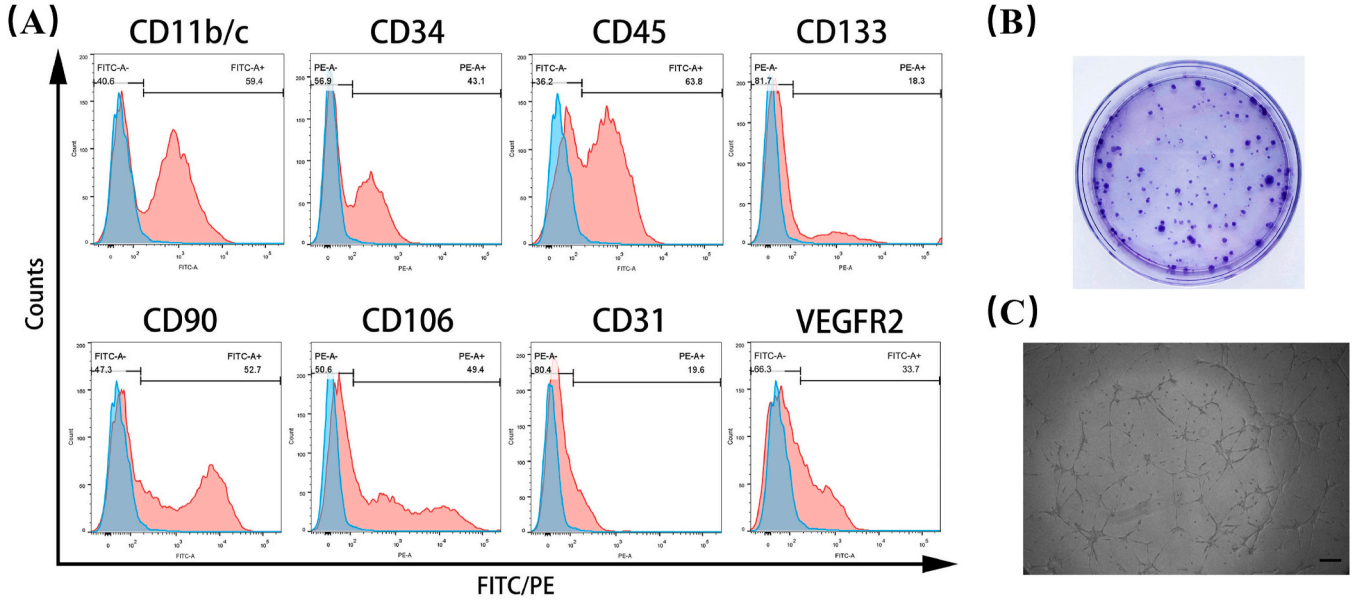

Fig. 11. (A) Flow cytometry analysis of the stromal vascular fraction (SVF). (B) The SVF was inoculated into culture dishes, stained, and its clonogenic potential was confirmed. (C) Representative photomicrographs depicting angiogenesis induced by SVF cells. Reproduced with permission [71]. Copyright Elsevier.

host vascular system upon implantation, thereby facilitating better tissue survival and function. The development of such pre-vascularized tissue constructs typically involves the creation of microvascular networks that can be integrated with the existing vasculature post-transplantation. Various approaches have been proposed for pre-vascularization, including the use of endothelial cells, angiogenic growth factors, and biomaterial scaffolds that support vascular network formation. However, achieving the complex architecture and physiological function of native vasculature remains a critical hurdle, necessitating further advancements in biomaterial design, bioreactor-based conditioning, and co-culture systems to improve in vivo functionality. Furthermore, the most promising technique currently is the design and generation of vascular networks using customizable 3D bioprinting techniques [73]. This approach allows for the precise placement of cells, growth factors, and extracellular matrix components in a spatially controlled manner, mimicking the natural architecture of blood vessels and significantly improving the potential for successful vascularization in tissue-engineered constructs. The versatility of 3D bioprinting also offers the ability to design complex vascular networks that meet the specific needs of various tissue types, making it a key tool in advancing the field of tissue engineering and regenerative medicine.

3.3. Anti-inflammatory

Inflammation can be triggered by a variety of factors, with infections caused by biological pathogens being a prominent cause. Infections remain a leading cause of death worldwide, and every year, millions of patients suffer from trauma, diseases, or infections that result in the loss of vital tissues such as skin, bone, nerves, cartilage, liver, and blood vessels. [74–76] Tissue engineering offers an option for these lesions [77]. However, microbial colonization remains a significant contributor to the failure of tissue-engineered grafts [75,78,79]. In the urinary system, urinary tract infections (UTIs) are the most common type of nosocomial infection [80]. Bacterial infections can induce scaling, which negatively affects the survival and functionality of tissue-engineered grafts. Therefore, investigating the antimicrobial properties of grafts is a crucial area for future research in urologic tissue engineering. In addition to infection-induced inflammation, the rejection of implanted biomaterials and the repair process itself can trigger inflammation, potentially leading to fibrotic reactions. Severe fibrosis can impair the in vivo function and longevity of implanted structures (see Fig. 12). Extensive localized fibrosis may also extend to adjacent organs and progress into the abdominal cavity, resulting in significant adhesions [81].

In their review, Adamowicz et al. proposed several potential solutions to address the challenges associated with fibrosis in implantable materials. First, they suggested intervening in the activation of fibrotic mechanisms from the very beginning, during the material design process. By implementing early-stage interventions, they believe that the initiation of fibrotic responses could be minimized, ultimately improving the long-term functionality and biocompatibility of the implant. Additionally, they recommended exploring the possibility of incorporating antifibrotic drugs directly into the implanted stent. This strategy could allow for localized, controlled release of antifibrotic agents at the site of implantation, potentially inhibiting the fibrotic response and enhancing the tissue integration of the stent. By addressing the fibrotic process at its core, this approach holds promise for improving the efficacy and durability of implantable devices. These proposed strategies offer valuable insights into how the design and pharmacological modification of implant materials can mitigate complications and improve clinical outcomes in tissue engineering and regenerative medicine [73].

It was discovered that transplantation of human urine-derived stem cells (USCs-Exo) in a mouse model of unilateral ureteral obstruction (UUO) led to the selective homing of these cells to damaged renal tissue. Furthermore, it was observed that the transplanted cells overexpressed the miRNA-let7c gene, which contributed to the effective alleviation of renal injury. The overexpression also resulted in a significant downregulation of collagen IVα1, metalloproteinase-9, TGF-β1, and the TGF-β1 receptor in the UUO kidneys. Consequently, an effective antifibrotic effect was observed, leading to the repair of renal injury. In vitro , experiments further confirmed that MSC-Exos overexpressing let7c significantly inhibited TGF-β1-induced upregulation of fibrotic gene expression in NRK52E cells [82].

Furthermore, the development of minimally invasive laparoscopic or robotic extra-abdominal grafting techniques presents an opportunity to reduce scar formation at the perioperative site and minimize the risk of severe abdominal adhesions [73].

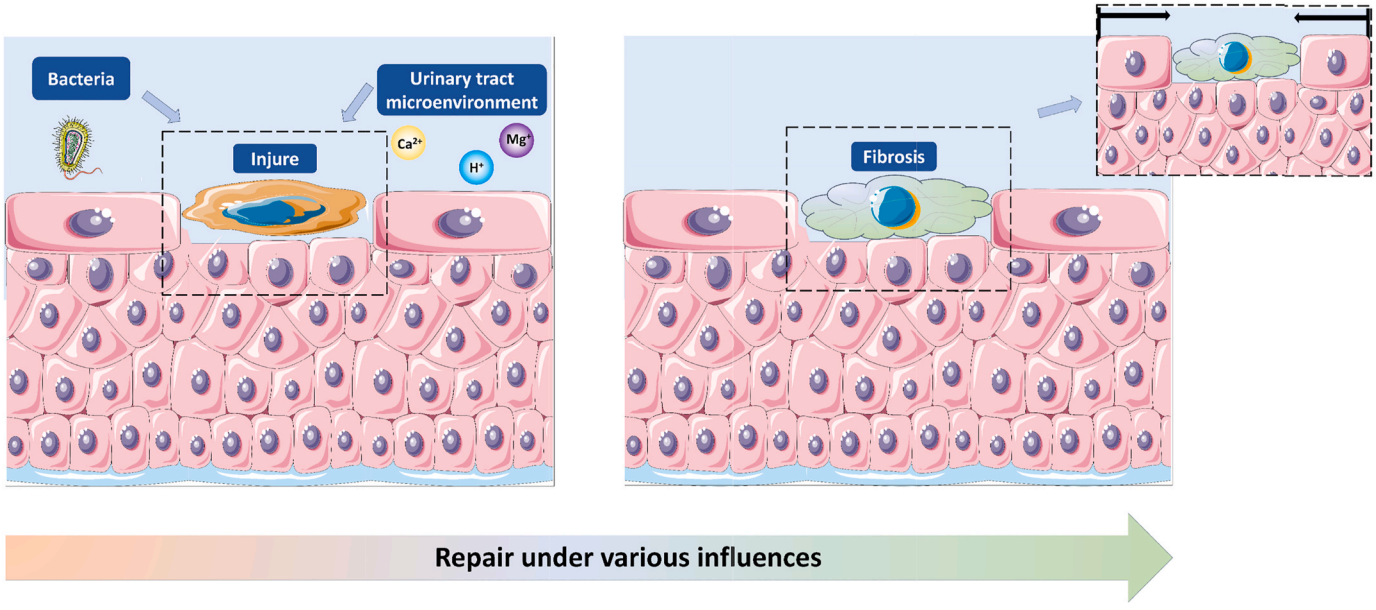

Fig. 12. Schematic diagram of fibrotic repair. Under the influence of bacterial infection and the urinary microenvironment, the affected tissues undergo fibrosis and repair, leading to a loss of their original contractile function.

3.4. Antitumor

Tissue engineering holds immense promise for the future treatment of cancer [83]. Urologic tumors are among the most common malignancies in humans, and their incidence is steadily increasing [84]. These tumors have been treated with various therapeutic approaches. For instance, chemotherapy and radiotherapy are the primary strategies for advanced renal cancer, while surgical treatment remains a key option for early-stage tumors. Advances in tissue engineering have significantly enhanced our understanding of urologic tissue repair, augmentation, and replacement, thereby improving the quality of life for countless patients. Beyond organ reconstruction, tissue engineering is increasingly integrated into cancer research to develop 3D structures for both molecular therapy development and drug screening, including testing for toxicity and radiation sensitivity [83,85–87]. In recent years, as tissue engineering has progressed, 3D culture systems have become a central area of research in tumor biology. These systems are widely used to establish intercellular connections and interactions between cells and the extracellular matrix in vitro, effectively mimicking the complex tumor microenvironment. This approach facilitates the creation of in vitro tumor models, which serve as invaluable tools for studying tumor biology, conducting drug screening, and developing targeted therapies (Fig. 13). [88].

A notable example of the application of 3D culture systems in urologic oncology is the development of patient-derived bladder cancer organoids (PDBCOs). These organoids, generated from tumor biopsies or surgical specimens, retain the genetic and phenotypic heterogeneity of the original tumor, making them highly representative models for studying tumor progression and therapeutic resistance [89]. Additionally, advanced bioprinting techniques have enabled the creation of

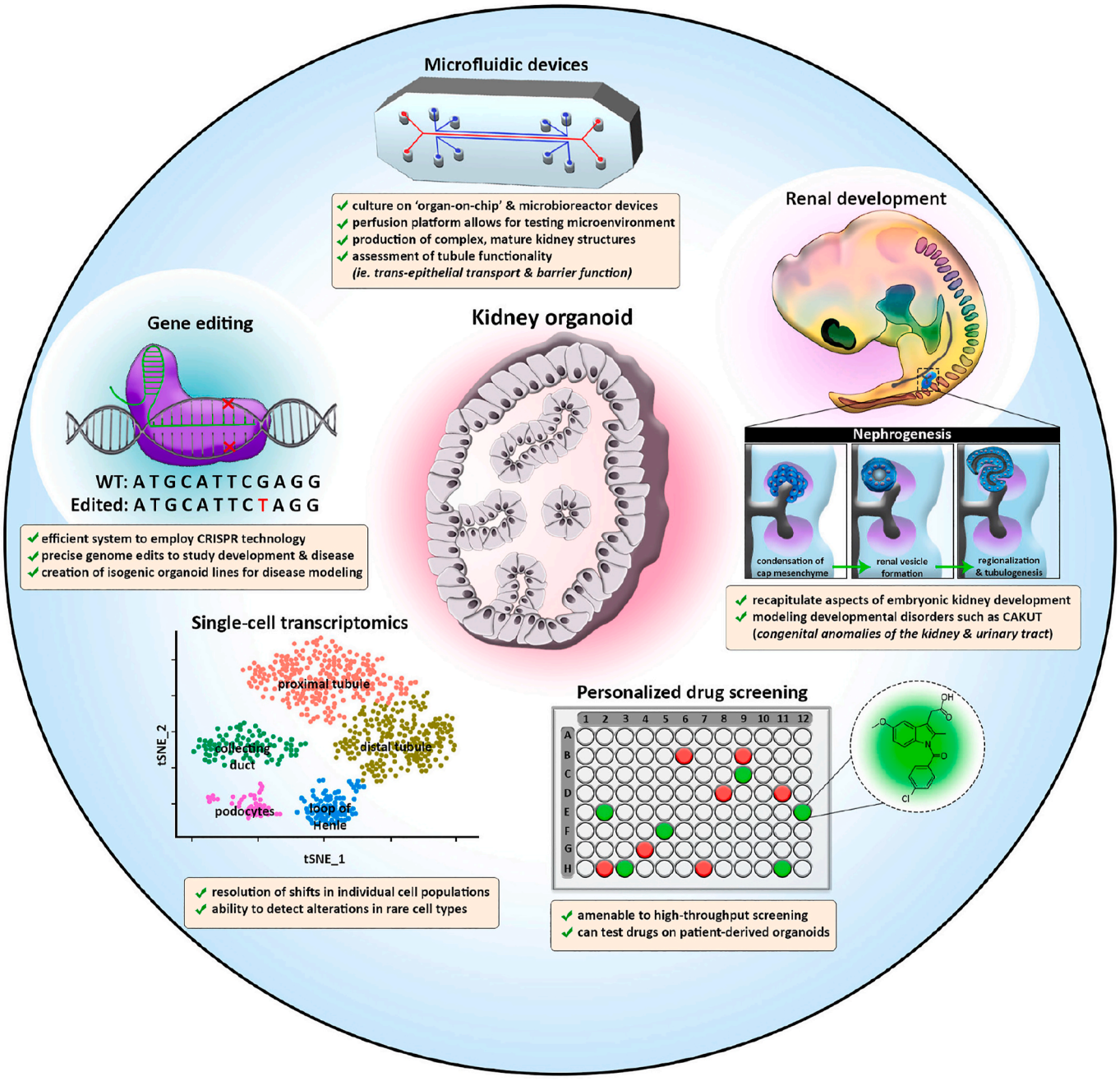

Fig. 13. Diagram illustrating evolving applications of kidney organoid technologies. Reproduced with permission [88]. Copyright MDPI.

vascularized bladder cancer models, incorporating endothelial cells and fibroblasts to mimic the tumor-stroma interface. These models have been instrumental in studying the role of angiogenesis in tumor growth and testing anti-angiogenic therapies. Furthermore, microfluidic-based tumor-on-chip platforms have been employed to replicate the dynamic mechanical forces of the urinary tract, providing insights into how fluid shear stress influences tumor cell invasion and drug delivery efficiency. These innovative models not only bridge the gap between traditional 2D cultures and in vivo studies but also offer a scalable platform for personalized medicine and high-throughput drug screening.

3.5. Neurogenesis

Neural tissue engineering demonstrates significant potential in repairing damaged neural tissue. Tissue engineering is recognized as a critical tool in the development of new neurological systems, especially in the repair of neural tissues. The lower urinary tract receives innervation from cholinergic, peptidergic, and azotinergic nerve fibers originating from the peripheral autonomic and somatic nervous systems [90]. Most functional issues of the urinary tract are linked to neurological injuries or defects in the peripheral or central nervous system. These issues typically result from spinal cord injury, pelvic trauma or surgery, infection, inflammation, degenerative diseases, congenital malformations, bladder outflow obstruction, or the effects of pregnancy and childbirth. Functional outcomes include the loss of autonomic control, abnormal reflex activity, dysfunctional sphincter synergism, stress incontinence, urge incontinence, and overactive bladder [91]. However, despite promising results in regenerating damaged neural tissues, tissue engineering approaches remain insufficient for achieving complete functional recovery from severe neurological injuries [92,93]. Therefore, neural network alternatives are necessary to re-establish upstream and downstream neuronal transmission and autonomic activity in the urinary system, thereby restoring normal organ function. Recent advances include biomimetic scaffolds (e.g., conductive hydrogels, neurotrophic topographies), stem cell-derived neural progenitors, and spatiotemporal delivery of neurotrophic factors (e.g., NGF, BDNF) to promote nerve regeneration. 3D bioprinting and electrical stimulation further enhance axon guidance. However, challenges remain in synchronizing neuro-tissue interfaces and modulating degenerative microenvironments. Future directions involve single-cell profiling to decode neural repair mechanisms, smart responsive scaffolds, and biohybrid systems integrating organoids with bioelectronics, advancing personalized urogenital tissue engineering.

4. Urinary tissue engineering

4.1. Bladder

The bladder exhibits complex anatomical and physiological functions that are essential for urine storage and release. This process requires the bladder's ability to contract and relax, along with a specialized inner layer capable of withstanding intraluminal pressure and varying urine volumes [32,94,95]. Additionally, the bladder features a multi-layered structure that works in concert with the external urethral sphincter to effectively store urine. Lining the bladder is a unique transitional epithelium, which plays a crucial role in protecting the underlying stroma from potential damage caused by urine exposure [96]. As previously mentioned, a variety of disorders necessitate bladder reconstruction and enlargement, with traditional surgical approaches often leading to significant complications [97–99]. Tissue engineering offers an alternative strategy to improve patient outcomes by potentially restoring the bladder wall's complex histological structure through the integration of epithelial, neural, and muscular components. This approach holds considerable promise as a more effective therapeutic option compared to current solutions. Traditional scaffolds, infused with cells and biological factors, have been extensively used in bladder repair, demonstrating efficacy in animal models. Tissue engineering provides new strategies for bladder tissue reconstruction. For example, Li et al. developed and evaluated a surgical patch incorporating adipose-derived stem cells (ADSCs), using various biomaterials, including acellular bladder matrix (BAM), type I collagen derived from rat tails, microemulsion cross-linked polylactic-hydro glycolic acid (PLGA)-chitosan (CS) combined with PLGA-sodium alginate (SA), and growth factors. In rats subjected to 50 % bladder resection, bladder repair was performed using this surgical patch. Histological, immunohistochemical, and urodynamic analyses were conducted at 2, 4, and 8 weeks post-surgery. The results demonstrated the regeneration of the urinary tract cortex, muscle fibers, and blood vessels, effectively replacing 50 % of the natural bladder tissue in vivo. Both qualitative and quantitative evaluations indicated that this composite biomaterial holds significant potential for bladder tissue repair and reconstruction [100]. However, the low survival rate of transplanted cells and the potential risk of rejection remain significant challenges, limiting the therapeutic efficacy of these approaches.

Recent studies have increasingly focused on non-cellular tissue engineering scaffolds aimed at enhancing tissue repair through the recruitment of autologous cells. One such material, the PC (Procyanidins)-SIS (small intestine submucosa) scaffold, developed by Zhang et al. (Fig. 14A), demonstrates excellent biocompatibility, mechanical properties, and anti-calcification activity. In rabbit model experiments, cystoplasty using the PC-SIS patch resulted in improved bladder function compared to the SIS patch, promoted smooth muscle regeneration, enhanced bladder compliance, and helped prevent the progression of renal disease [101]. This PC-SIS material holds significant potential as a bladder patch for facilitating smooth muscle regeneration and promoting the recovery of bladder function (Fig. 14B and C).

Zhao et al. developed a synthetic nano-scaffold system consisting of stromal vascular fraction (SVF) secretome (Sec) loaded onto zeolite imidazolate framework-8 (ZIF-8) nanoparticles, which were subsequently integrated into a bladder decellularized matrix (Fig. 14D). This artificially decellularized nanocomposite scaffold (ANS) can be cryopreserved for long-term storage and exhibits gradual degradation, enabling the slow release of SVF-Sec to support tissue regeneration. BAM or ANS were implanted subcutaneously in rats, and grafts were harvested 2 weeks later to assess vascularization. Immunofluorescence staining with anti-CD31 antibody revealed that the microvascular density in both low-temperature preserved and freshly synthesized ANS groups was significantly higher than in the BAM or empty ANS groups (Fig. 14E). In a rat model, ANS transplantation exhibited strong pro-angiogenic potential and induced M2 macrophage polarization. Histological analysis demonstrated that urothelium and smooth muscle regenerated or developed into a complete bladder wall structure, comprising multiple layers of urothelium, a prominent lamina propria, and smooth muscle bundles (Fig. 14F and G). These findings suggest that ANS promotes tissue regeneration and aids in restoring bladder function [71]. Due to its stem cell-like effects and the ability to overcome survival challenges associated with traditional stem cells, ANS holds promise as a clinical alternative for bladder regeneration, offering an innovative solution compared to cell-bound scaffold models.

Studies have shown that urothelial stem cells (USCs), which share a high degree of similarity with the urinary system, exhibit superior adaptability to the bladder environment in vivo. Consequently, they are regarded as an ideal cell source for bladder tissue regeneration and reconstruction. Furthermore, USCs are thought to originate from renal tubules or renal papillae, with the ability to differentiate into both smooth muscle (mesodermal origin) and urothelial (endodermal origin) cell lines in vitro. Song et al. developed an SIS scaffold (AC-SIS) that binds to anti-CD29 antibodies, enabling the specific capture of USCs for tissue repair and regeneration (Fig. 15A). These scaffolds demonstrated effective capture capability and favorable biocompatibility. In a rabbit bladder repair model, the control group exhibited bladder wall thinning during bladder filling, significant bladder enlargement, and reduced

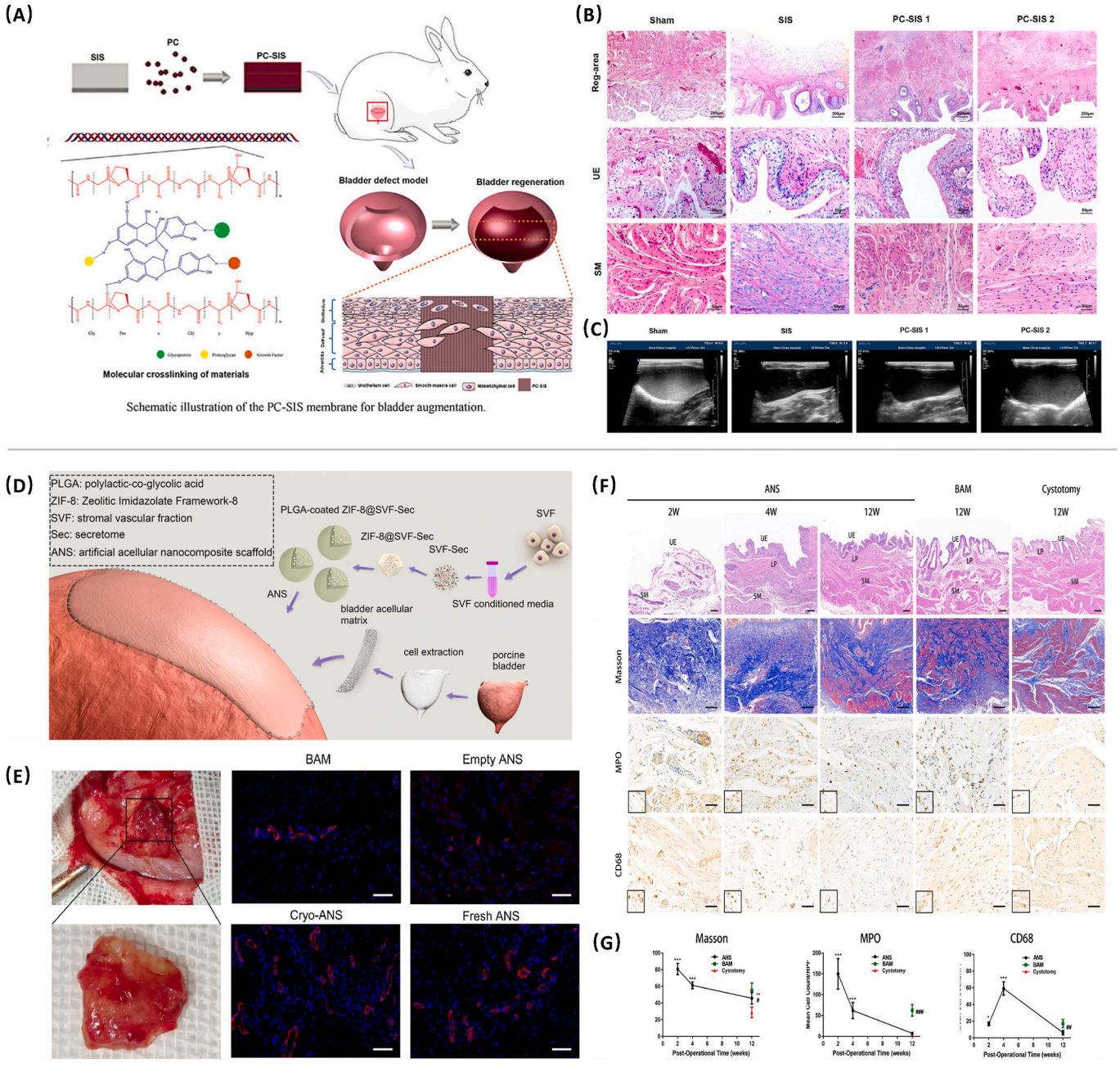

Fig. 14. (A) Synthesis of the PC-SIS membrane and schematic diagram illustrating bladder augmentation for the repair of a full-thickness bladder defect in a rabbit model. (B) Histological and morphological observations of the regenerated bladder in both the sham operation group and the experimental group. H&E staining of the central region of the bladder showing the urothelium (UE) and smooth muscle (SM). (Scale bar:50 μm (C) Ultrasound images comparing bladder characteristics across different groups 12 weeks post-surgery. (D) Schematic diagram of the synthesis of ANS scaffolds and their role in bladder repair. (E) After two weeks of subcutaneous implantation of BAM or ANS, the expression of CD31 (red) was evaluated through both macroscopic photographs and micrographs. (Scale bar:50 μm) (F–G) Histological staining and analysis of the bladder wall at various time points following bladder reconstruction in rats. (Scale bar:200 μm) Reproduced with permission [71]. Copyright Elsevier. Reproduced with permission [101]. Copyright Elsevier. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

elasticity compared to normal tissue. In contrast, the SIS group had the largest bladder size, while the AC-SIS group maintained some bladder wall thickness, with bladder size closest to normal (Fig. 15B). During postoperative recovery, the control group showed near-complete wound healing within the first week, whereas the experimental groups displayed full coverage of the scaffold material. Two weeks after surgery, both the SIS and AC-SIS groups showed substantial healing, with significant tissue thickening and submucosal edema. Bladder stones were present around the sutures in all experimental groups, but these disappeared as the sutures and materials degraded. By the fourth week, all experimental groups had significantly degraded scaffolds (Fig. 15C). Histological analysis further confirmed the efficacy of AC-SIS in bladder repair. H&E staining revealed significant neovascularization at the defect margin one-week post-surgery, with epithelial growth and angiogenesis observed by two weeks in the control group. In contrast, the AC-SIS group exhibited a considerable number of neovessels during this period. Eight weeks post-surgery, the AC-SIS group displayed a distinct hierarchical structure with well-defined smooth muscle fibers,

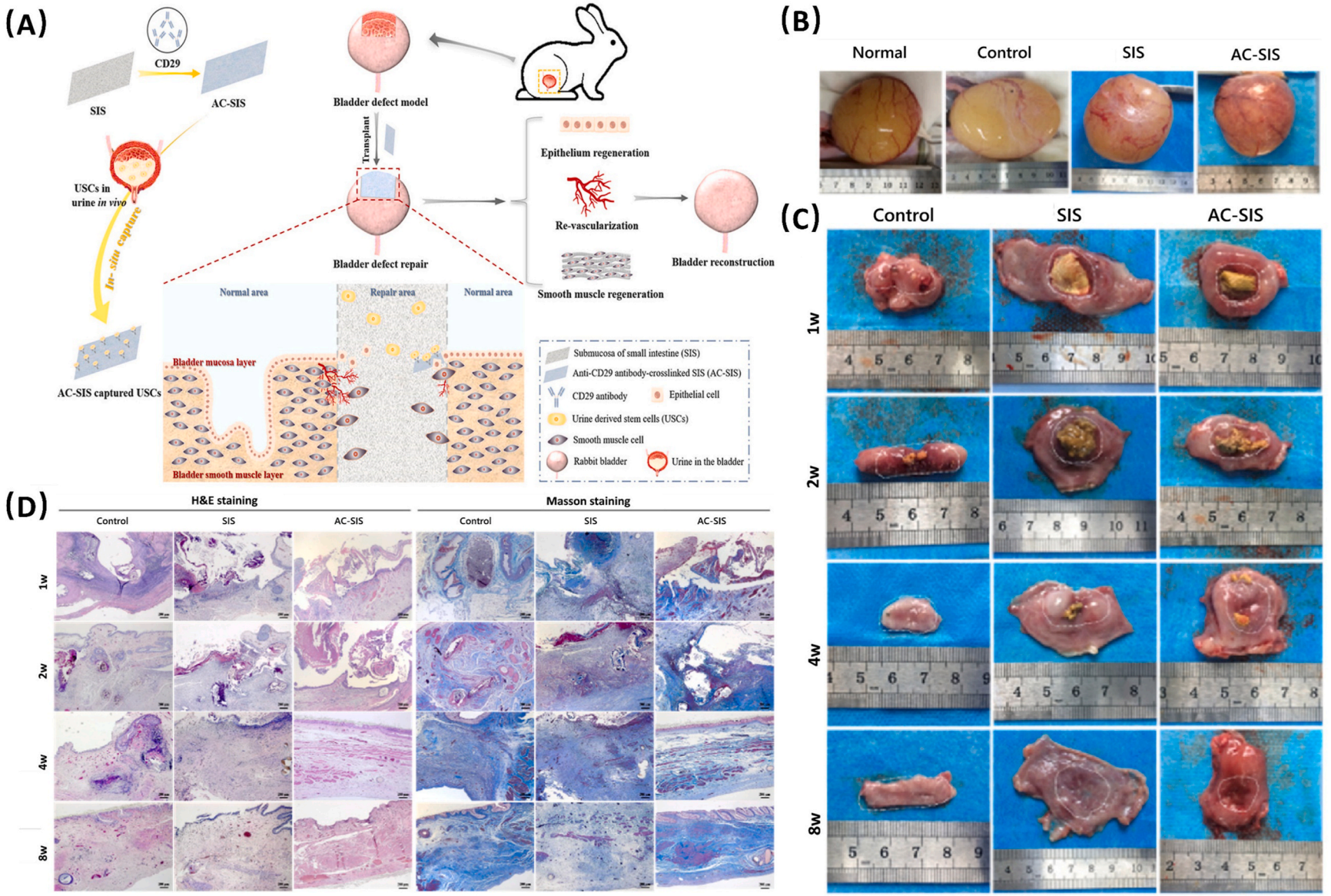

Fig. 15. (A) Synthesis of an anti-CD29 antibody-conjugated SIS scaffold (AC-SIS) and a schematic diagram illustrating its role in bladder repair. (B) Representative gross images of the regenerated bladder at 1, 2, 4, and 8 weeks post-repair in rabbits. (C) Representative images showing bladder filling at week 8 in each group. (D) Representative histological images of the regenerated bladder with H&E and Masson staining. (Scale bar: 200 μm) Reproduced with permission [102]. Copyright Elsevier.

showing annular fluctuations in the urinary tract cortex resembling normal urinary epithelium. This contrasted sharply with the control and SIS groups, which showed disorganized bladder urothelium and irregular smooth muscle-like tissue. Masson staining further supported these findings. Four weeks post-surgery, both the AC-SIS and SIS groups exhibited extensive collagen formation, with significantly higher collagen density than the control group. Moreover, small longitudinal and/or annular muscle bands, indicating enhanced tissue hierarchy and regenerative structures, were observed in the AC-SIS group. These differences became increasingly evident over time. By eight weeks, the collagen in the control group was densely arranged with no associated muscle fibers, whereas loosely distributed smooth muscle bundles were present in the SIS group. In the AC-SIS group, however, both collagen fiber density and the prominence of smooth muscle bundles increased (Fig. 15D). This may be attributed to AC-SIS's ability to capture USCs and thereby alter the microenvironment. In vivo experiments have demonstrated that AC-SIS scaffolds promote rapid endothelial healing and smooth muscle regeneration, offering promising opportunities for bladder reconstruction [102]. The use of a cell-free scaffold with specific USC capture capabilities presents significant potential for advancing tissue regeneration, holding considerable promise in the field of regenerative medicine.

Due to the biomechanical properties of the bladder and the physiological requirements for its optimal function, the clinical outcomes of bladder tissue engineering remain unsatisfactory. Current research is focused on refining scaffold selection and preparation, advancing nanotechnology approaches, and exploring stem cell-derived biology to enhance outcomes [37,103]. Future investigations will prioritize the development of functional vascular networks within the graft to mitigate complications related to ischemia, thereby improving the feasibility of bladder tissue engineering [104–106]. Simultaneously, it is crucial to explore superior biological materials that can better mimic the natural tissue environment, as well as enhance nerve regeneration technologies to facilitate functional recovery of neural control. These advancements are expected to improve both the mechanical properties and biocompatibility of the repaired tissues, increasing the survival rate and functionality of tissue-engineered grafts. Furthermore, the incorporation of multi-disciplinary approaches, including bioinformatics and 3D bioprinting, will accelerate the development of more precise and personalized solutions for bladder repair. Ultimately, these improvements will provide both theoretical and practical foundations for the successful clinical application of bladder tissue engineering, offering promising prospects for patients with bladder dysfunction and trauma.

4.2. *Urethra*

Owing to the substantial disparities between the male and female urethra, the male urethra consists of anatomically and functionally distinct segments, including the prostatic, membranous, and spongy urethra [107,108]. The female urethra is comparatively short, measuring 2.5–5 cm in length, and is more susceptible to infections due to its proximity to the external environment. The urethra may be impacted by various pathological processes that can substantially affect the quality of life and potentially cause organ damage (Fig. 16). The urethra can be affected by various pathological processes that have the potential to significantly impact the quality of life and even result in organ damage [109,110]. Surgical intervention is the primary treatment for urethral strictures. However, there is an increased risk of recurrence

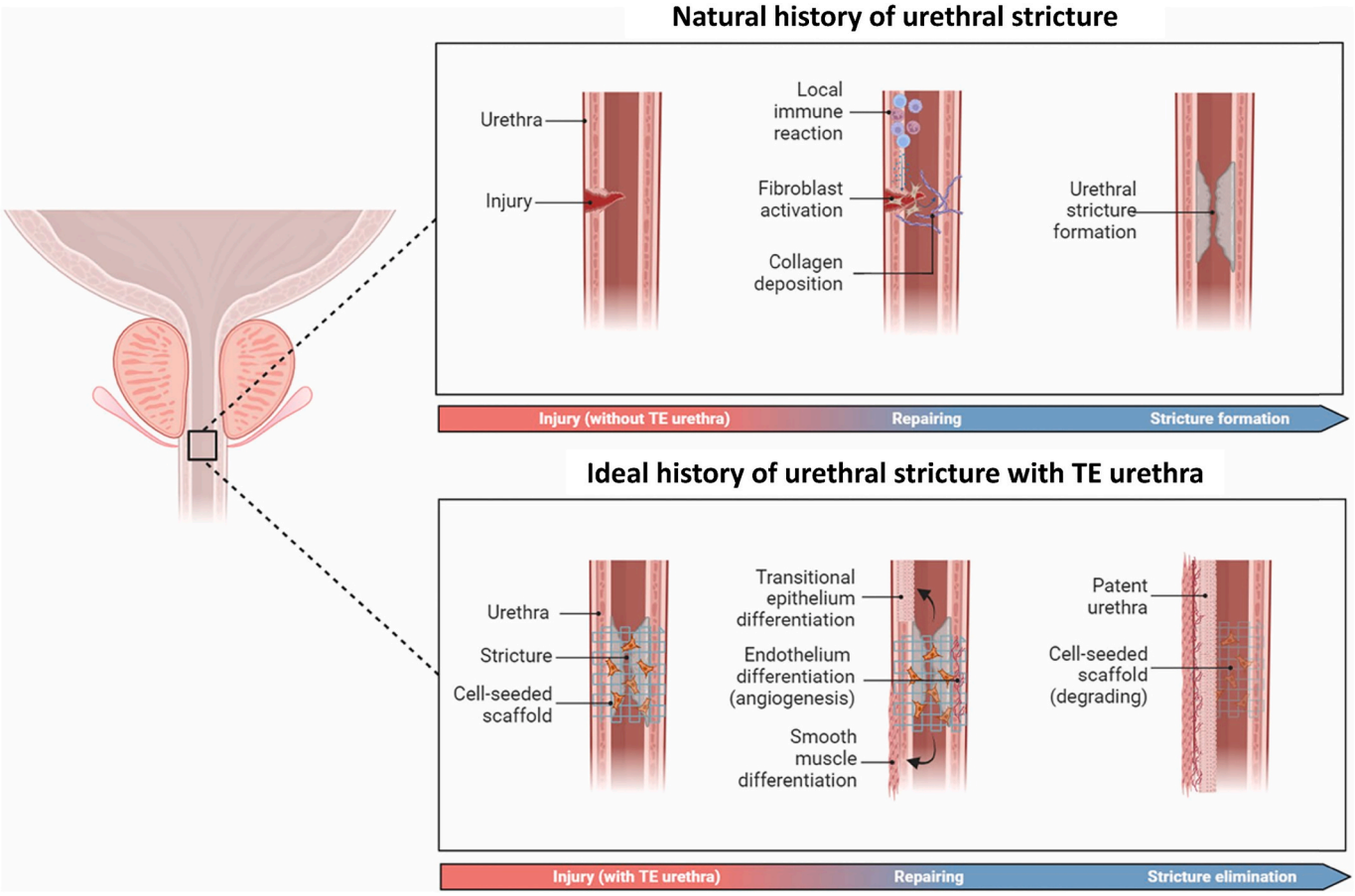

Fig. 16. The natural healing process of urethral stenosis and the optimal outcomes following surgical repair. Reproduced with permission [59]. Copyright Springer Nature.

as the length of the stricture extends [111–113].

Advancements in tissue engineering have the potential to address current limitations, improve prognostic outcomes, and reduce complications. Zhou et al. developed a 3-layered tissue-engineered urethra by layering cell sheets into tubular structures (Fig. 17A). In an experiment involving penile urethral tube replacement in dogs, retrograde urethrography was performed three months after urethral reconstruction to evaluate the condition of the urethra. Severe urethral stenosis was observed in the SIS implant group, while both the bionic urethral implant group and the buccal mucosa implant group exhibited characteristics resembling those of a normal urethra. Gross examination revealed significant scarring and contracture at the transplant site in the SIS implant group. In contrast, no ulcers, strictures, or fistulas were observed in either the bionic urethra implant group or the buccal mucosa implant group. Histological analysis conducted three months post-surgery revealed that the bionic urethral transplant closely mimicked normal urethral structure, with a well-organized, multi-layered tissue architecture. In contrast, the SIS group exhibited unclear tissue architecture, inadequate epithelial coverage, and fibrosis, suggesting suboptimal repair of the urethra. The buccal mucosa implant group demonstrated proper stratified epithelium covering the graft site, without signs of stenosis (Fig. 17B). USPIO labeling and MRI tracking experiments confirmed the successful construction of three cell sheets, which could be superimposed and tracked in vivo via MRI (Fig. 17C, D, E). Moreover, immunofluorescence analysis revealed the formation of a dense vascular network in the bionic urethra [49]. This approach may significantly improve the efficacy of urethral repair surgery, offering a promising alternative for urethral reconstruction.

In the field of urethral reconstruction, Juul et al. recently developed an optimized scaffold composed of high-density collagen and submerged

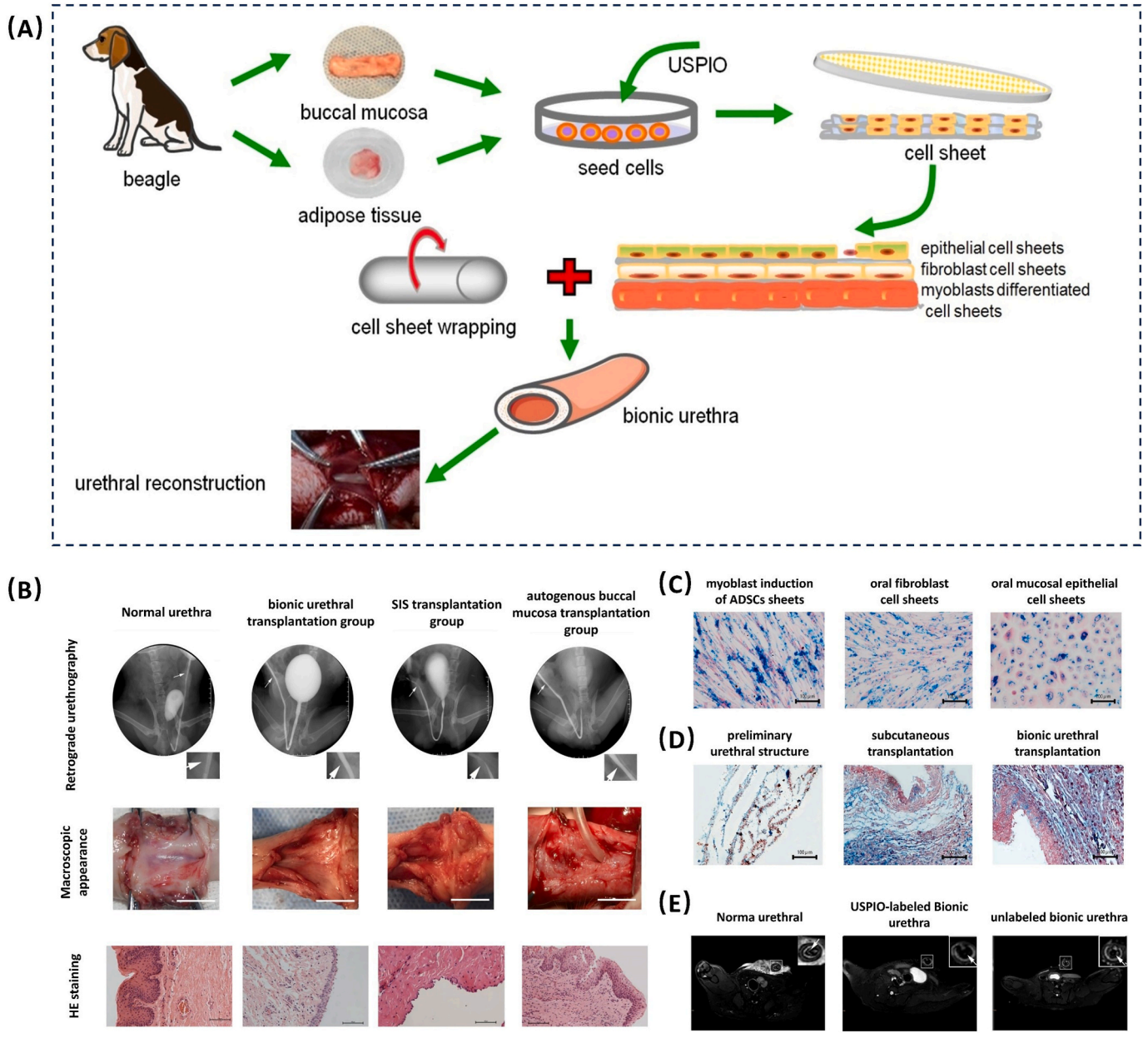

Fig. 17. (A) Diagram of tissue engineering for a bionic urethra utilizing cell sheet technology. At 3 months after full-thickness urethral reconstruction in dogs: (B) Retrograde urethrography, postoperative macroscopic appearance of the urethra (scale bar: 1.0 cm), and histological staining (scale bar:100 μm) were used to evaluate the urethra across the four groups. (C–E) In vivo USPIO labeling (scale bar:1.0 cm) and MRI tracking. Reproduced with permission [49]. Copyright Ivyspring International Publisher.

autologous micrografts, reinforced with mesh and scaffolds in vitro (Fig. 18A, B, C). This scaffold was successfully implanted into a mini-pig in vivo model (Fig. 18D). Three weeks post-implantation, immunohistochemical analysis revealed good host integration with the multilayered luminal uroepithelium within the catheter (Fig. 18E). [114] These findings provide support for the potential use of this technique in broader preclinical large animal studies and hold promise for future clinical applications.

3D bioprinting holds great potential in urethral tissue engineering, enabling the precise construction of complex urethral structures with localized control over the cell, scaffold, and growth factor distribution. Yang et al. developed UME-responsive composite hydrogel patches using multilayer 3D bioprinting with a sodium alginate (SA) backbone crosslinked with silicon quantum dots (SiQD) and nanoscale hydroxyapatite (nHA), incorporating ADSCs. These patches respond to Ca^{2+} in urine, promoting structural remodeling, inhibiting swelling, and enhancing scaffold strength. Immunofluorescence staining (AE1/AE3, CD31, PCNA, CD206) indicated that the patches enhanced wound healing through epithelialization, angiogenesis, cell proliferation, and inflammation regulation. Additionally, they activated collagen-related genes (e.g., MMP-1, COL3A1), while suppressing fibrosis-related genes (e.g., TGF-β/Smad) and mechanosensitive genes (YAP/TAZ), fostering myofibroblast activation and collagen deposition, which prevented fibrosis and promoted scar-free healing [115].

Urethral injury repair is a complex process, with inadequate healing leading to scar tissue formation. Fang et al. developed a hydrogel that promotes both healing and tissue regeneration. During the hemostatic phase, the hydrogel's collagen facilitates blood clotting and wound stabilization. In the inflammatory phase, LL-37 antimicrobial peptides provide antibacterial effects and modulate immune responses, creating a favorable environment for repair. In the proliferative phase, the dECM layer on ADSCs provides growth factors that enhance tissue regeneration and angiogenesis. These phases overlap and are interconnected, with the hydrogel regulating healing at multiple stages to guide overall repair. A rabbit urethral injury model was used to evaluate the hydrogel's effectiveness (Fig. 19 A). Gross evaluation showed significant scar formation in the control, APF, and APF/C groups 4 weeks post-injury, leading to USD. In contrast, the APF/C/L hydrogel group showed reduced scarring, likely due to LL-37's early anti-inflammatory effect. The APF/C/L@dECM group demonstrated the best repair, with a smooth, scar-free urethra (Fig. 19 B). Urethrography revealed severe lumen narrowing in the control, APF/C, and APF/C groups due to scar formation, while the APF/C/L group exhibited some obstruction. The APF/C/L@dECM group showed the least blockage and the highest Qmax, similar to the normal group (Fig. 19C and D). These results suggest effective healing with minimal scarring and no fistula formation in the APF/C/L@dECM group. Histological analysis showed disorganized structures and fibroblast infiltration in the control, APF, and APF/C groups. Scar tissue was reduced in the APF/C/L group at 4 weeks, but persisted at 8 weeks. Masson staining showed significant collagen deposition. In the APF/C/L@dECM group, urethral tissue exhibited normal structure with neatly arranged cells and collagen fibers, and no significant inflammation

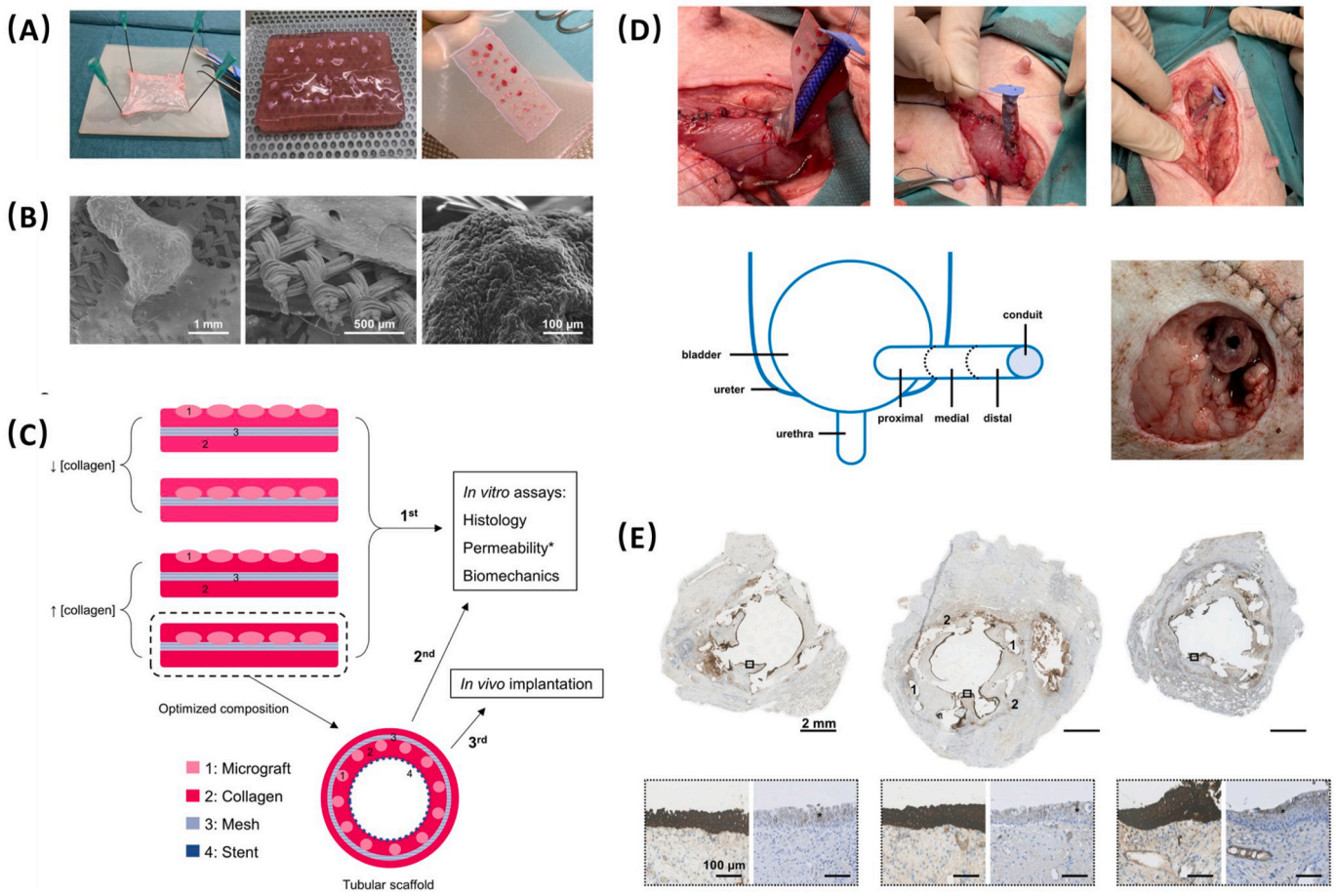

Fig. 18. In vitro study design and scaffold composition. (A) Urothelial anatomy of the pig bladder. (B) Scanning electron microscopy (SEM) images of the urothelial micrograft (left), compressed and embedded with collagen mesh (middle), and after 2 weeks of culture, urothelial cells migrated to the scaffold (right). (C) A schematic illustrating the initial study conditions for evaluating the optimal stent composition. (D) In vivo surgical implantation of micrograft catheters. (E) Cross-sectional specimens obtained from the proximal, medial, and distal regions of the catheter after three weeks in vivo. The specimens underwent CK-AE staining followed by Uroplakin-II staining. Reproduced with permission [114]. Copyright Springer Nature.

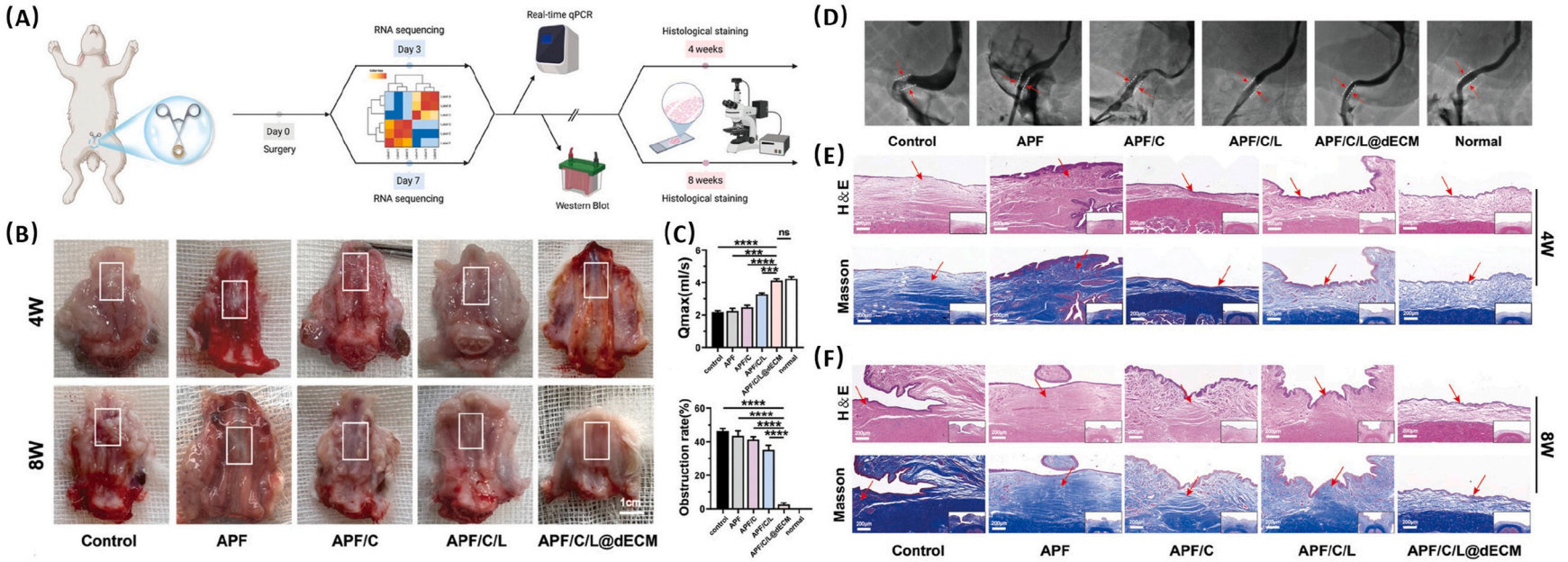

Fig. 19. (A) Schematic diagram illustrating the complete repair process of urethral injury in rabbits treated with hydrogel. (B) General photographs taken at various time points following surgery across different experimental groups. (C) Qmax values and urethral obstruction rate. (D) Rabbit urethrogram (E, F) H&E and Masson staining micrographs (scale bar: 200 μm) taken at 4 and 8 weeks post-injection of various hydrogels. Reproduced with permission [116]. Copyright John Wiley and Sons.

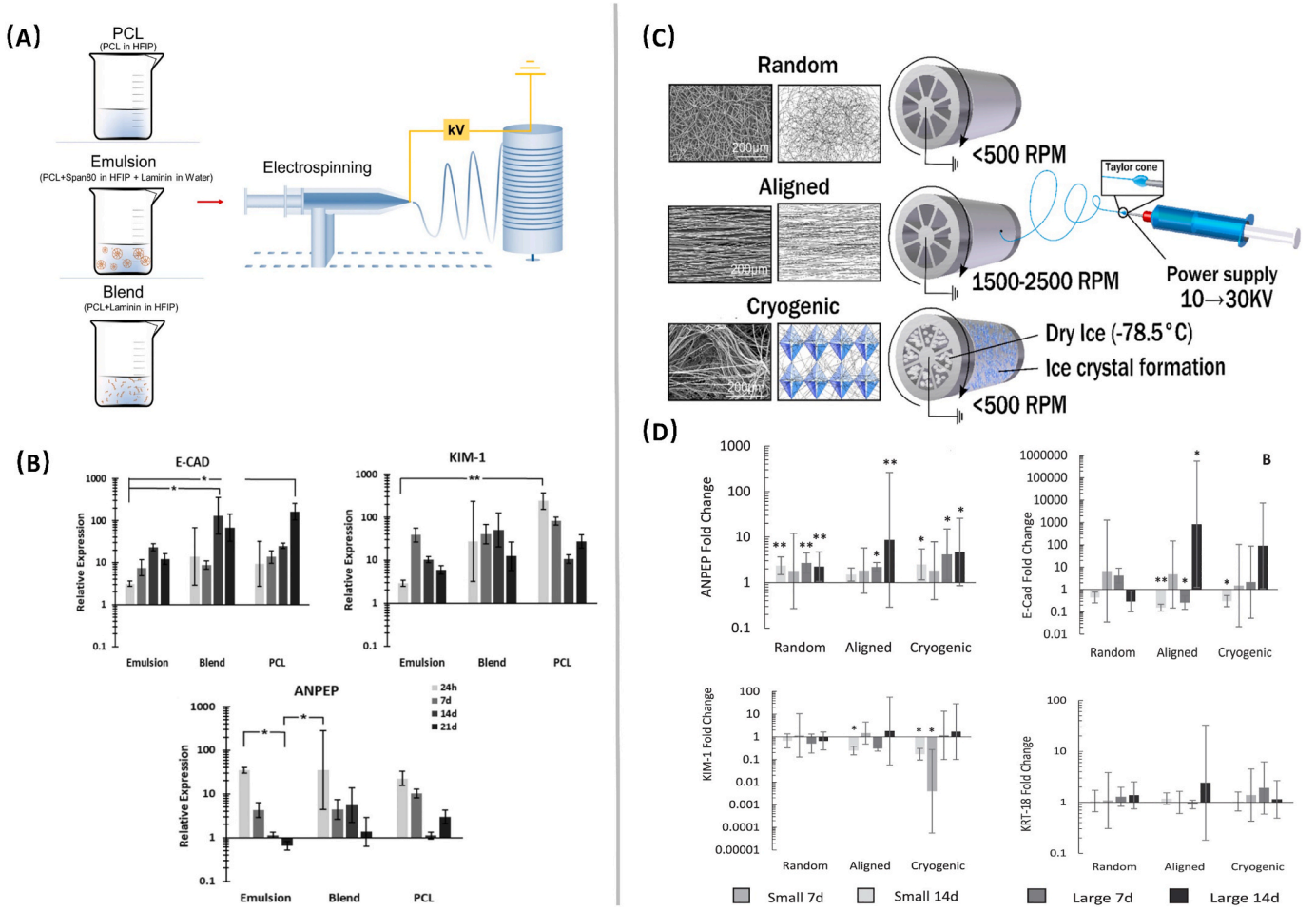

Fig. 20. (A) Schematic representation of scaffold fabrication. (B) Gene expression analysis: RT-qPCR analysis showed the expression levels of E-CAD, KIM-1, and ANPEP. (C) Schematic diagram of electrospinning methods: Illustration of the techniques used to fabricate electrospun fibers with varying structures. (D) Gene expression analysis: RT-qPCR analysis demonstrated the expression levels of ANPEP, E-CAD, KIM-1, and KRT-18. Reproduced with permission [4]. Copyright Spring Nature. Reproduced with permission [123]. Copyright IOP Publishing.

(Fig. 19E and F) [116].

Tissue engineering offers significant potential for the treatment of urethral stricture disease. Animal model studies have demonstrated the promising potential of tissue-engineered urethras regarding both functionality and biocompatibility. Several studies have confirmed their efficacy in repairing urethral defects, with favorable outcomes. Some cases have undergone clinical testing, which preliminarily suggests the feasibility of their application in humans. However, further validation is necessary to evaluate long-term effects and support widespread implementation. While significant progress has been made in developing safe and reliable tissue-engineered grafts, a deeper understanding of the failure mechanisms and risk factors associated with various graft materials and designs is needed, particularly in relation to urethral physiological characteristics and environmental factors. The development of advanced smart materials and devices capable of monitoring and responding to microenvironmental changes in vivo could establish more sophisticated urethral tissue engineering platforms. These innovations are expected to facilitate dynamic regulation, thereby supporting fundamental research, preclinical studies, and personalized therapies.

4.3. Kidney

Chronic kidney disease (CKD) is a highly lethal condition worldwide and is projected to become the fifth leading cause of death by 2040 [117]. The primary treatment options for CKD are dialysis and kidney transplantation. However, due to the short lifespan of transplanted kidneys, many patients require a second transplant, which significantly impacts their quality of life, especially given the limited availability of suitable donors [14,118]. The kidney presents unique challenges for treatment due to its complex 3D structure, specialized compartments, extensive vascularization, and diverse cell types with distinct physiological functions [119,120]. If the nephron is damaged, it cannot regenerate [121]. Therefore, an effective scaffold with adequate stability, porosity, and biocompatibility is crucial to support renal cell differentiation, nephrogenesis, and organ vascularization [122].

Electrospinning is a promising technique with great potential for creating physiological microenvironments for various tissues, particularly in renal tissue engineering [14]. Baskapan et al. employed hybrid and emulsifying electrospinning methods to produce innovative scaffolds made from polycaprolactone (PCL) and laminin (Fig. 20A). The incorporation of laminin improved the scaffold's elasticity and enhanced both cell-to-cell and cell-to-fiber interactions. Gene expression analysis of E-CAD, KIM-1, and ANPEP showed that the hybrid scaffold effectively supports renal cells and provides a favorable environment for their growth (Fig. 20B) [4]. Similarly, Burton et al. developed a novel PCL scaffold with varying structures and porosity using electrospinning and low-temperature electrospinning techniques (Fig. 20C). This study demonstrated that the scaffold exhibited favorable hydrophilicity and specific mechanical properties. Furthermore, it was found that larger fiber diameters promoted increased cell adhesion, viability, and alignment. Notably, the upregulation of ANPEP, a key marker of proximal tubular epithelial cells, was also observed in this study (Fig. 20D) [123].

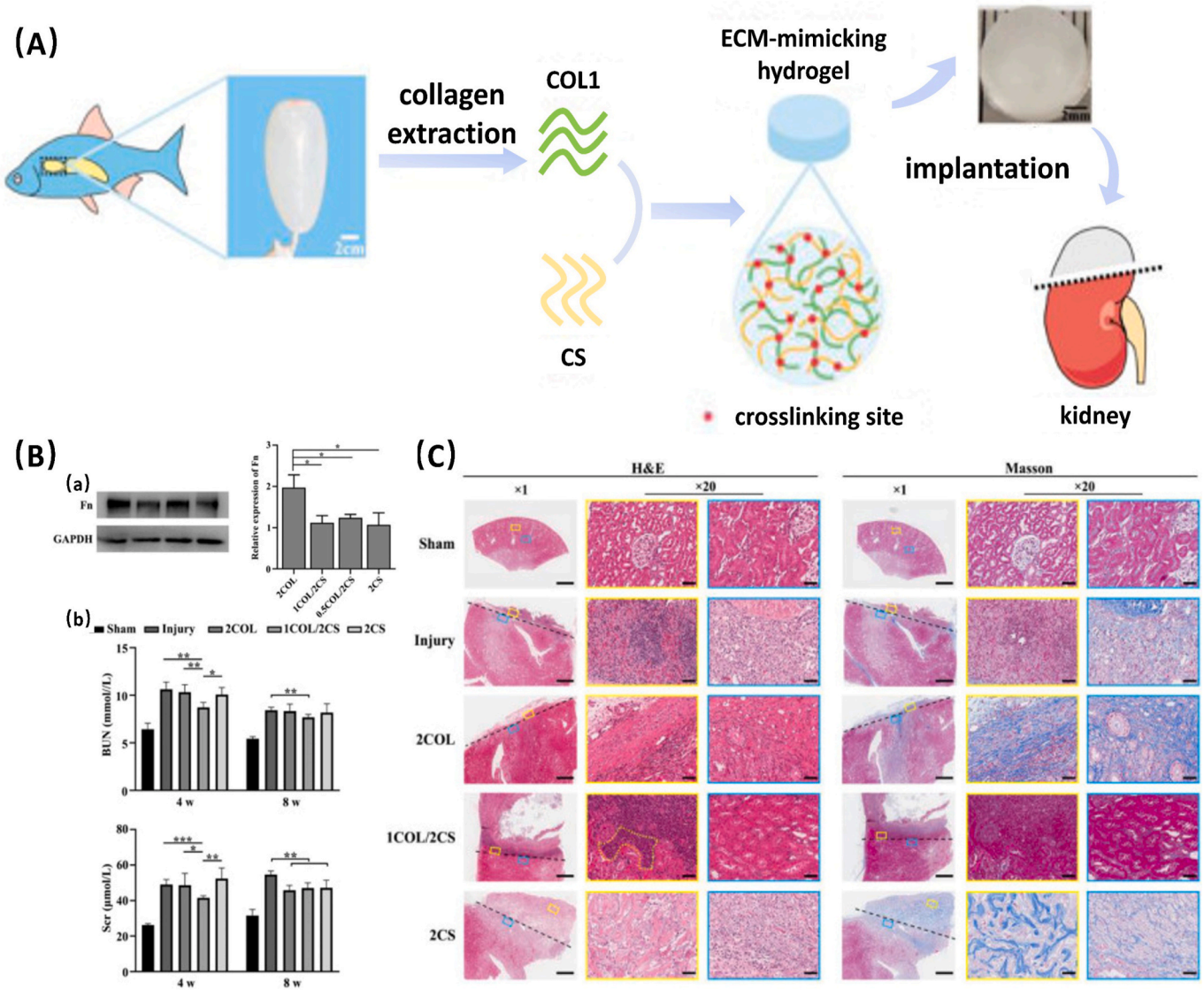

Fig. 21. (A) Diagram of the preparation of a novel hydrogel scaffold material that mimics the extracellular matrix and is used for renal regeneration. (B) a: Western blot analysis and quantitative assessment of fibronectin protein expression in renal mesangial cells (RMC) cultured on the biomimetic porous hydrogel for 3 days in vitro, b: Renal function in rats was evaluated by measuring blood urea nitrogen (BUN) and serum creatinine (Scr) concentrations at 4 and 8 weeks post renal repair. (C) Histological analysis: Postoperative tissue samples were stained with Hematoxylin and Eosin (H&E) and Masson's Trichrome to assess renal tissue regeneration in vivo following partial nephrectomy in rats. The dashed line indicates the site of surgical resection. The dashed line indicates the site of surgical resection. (× 1, scale bars:1 mm; × 20, scale bars:50 μm) Reproduced with permission [125]. Copyright Elsevier.

Hydrogels are a class of physically or chemically crosslinked polymer materials characterized by high hydrophilicity, excellent biocompatibility, and soft mechanical properties that closely resemble living tissues. Due to their ability to mimic both the structure and function of the kidney, hydrogels are considered ideal candidates for efficient kidney replacement therapies [124]. Wu et al. developed an extracellular matrix-mimicking hydrogel using polysaccharides, chitosan (CS) , and collagen type I (COL I), extracted from the swim bladder of grass carp for renal repair following nephrectomy in mice (Fig. 21A). Western blot analysis showed high levels of fibronectin (Fn) protein expression. Compared to injured rats without stent grafts, those implanted with a 1COL/2CS scaffold exhibited significant improvements in renal function, as evidenced by reduced serum creatinine (Scr) and blood urea nitrogen (BUN) levels (Fig. 21B). Histological analysis revealed that the 1COL/2CS hydrogel, with its porous network, formed a neonatal renal tubule-like structure at the nephrectomy site. No fibrosis or other damage was observed in the native renal tissue, indicating that the 1COL/2CS hydrogel not only demonstrates high biocompatibility but also promotes good cell adhesion and possesses anti-fibrotic properties, which are crucial for effective in situ renal repair (Fig. 21C) [125]. Therefore, hydrogels hold significant potential as scaffolds for renal tissue engineering and drug delivery due to their high porosity, specific surface area, and degradability as carrier materials. At the same time, emerging strategies such as spatiotemporally controlled photopatterning to modulate hydrogel mechanics and machine learning-guided design of multi-scale architectures may hold promise for reconciling biocompatibility with the mechanical demands of kidney function, enabling improved structural stability and functional integration.

3D organoids possess the ability to closely resemble physiological tissues and partially mimic organ function, making them valuable models for a broad range of applications, from developmental and stem cell research to personalized medicine (Fig. 22) [126]. In renal tissue regeneration, simple blocks consisting of a single cell type in an in vitro 3D environment have been used to model renal diseases like polycystic kidney disease (PKD), conduct preclinical drug screening for

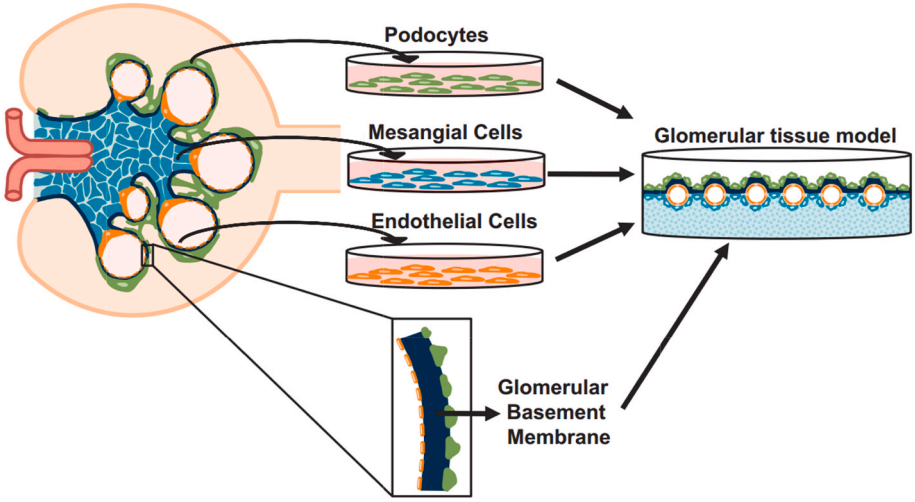

Fig. 22. Schematic diagram of the glomerular tissue engineering model. Reproduced with permission [126]. Copyright Elsevier.

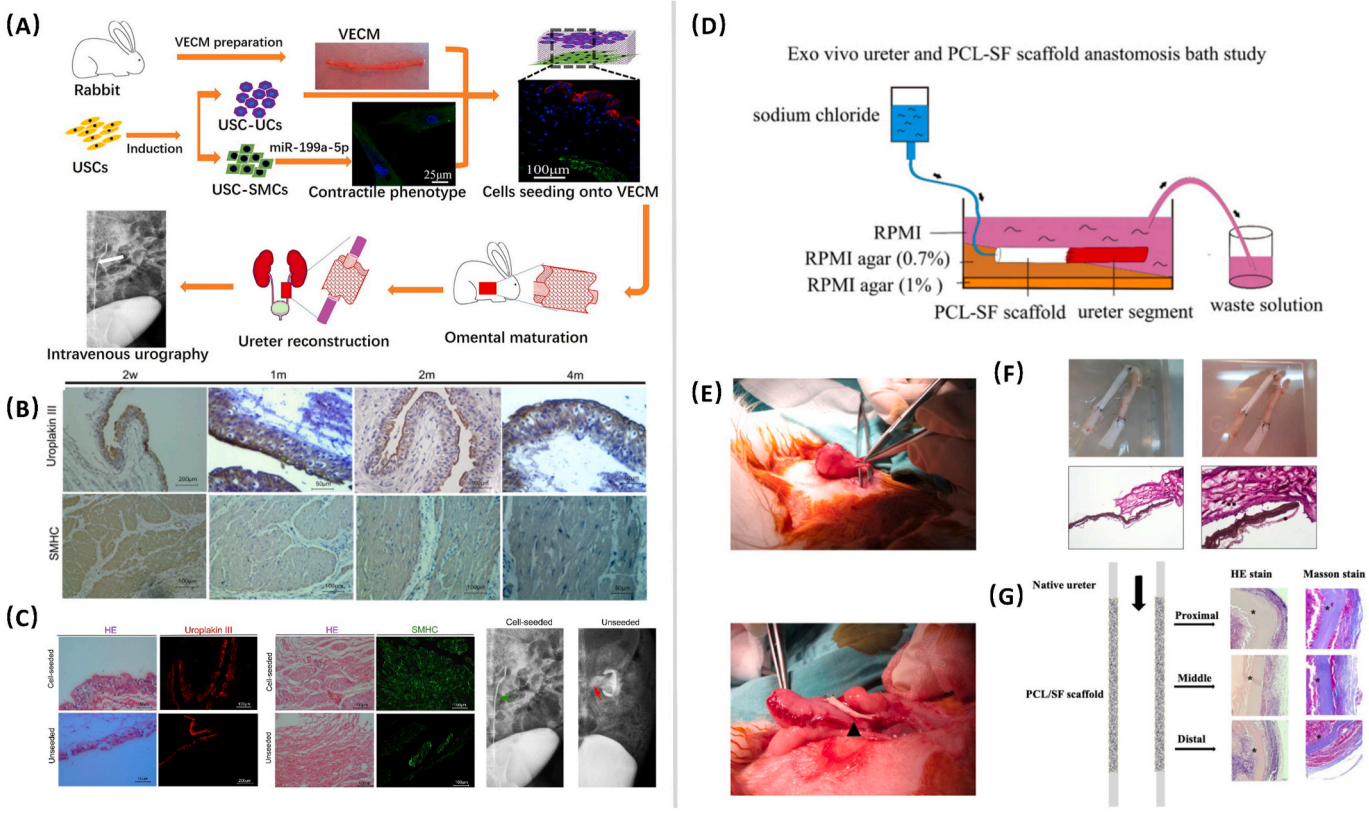

Fig. 23. (A) Diagram illustrating the preparation and application of VECM in ureteral reconstruction (B) Urethral epithelium and smooth muscle regeneration at different time points (IHC staining). The urinary tract cortex is marked by UP III. The smooth muscle layer is labeled by SMHC. (C) Comparison of urethral epithelium and smooth muscle formation between seed cell scaffolds and non-seed cell scaffolds two months post-ureteral reconstruction surgery, accompanied by venous urography images. (D) Schematic illustration of long-term ex-vivo agar bath culture of segmental ureter tissue with PCL-SF scaffold anastomosis. (E) exploration of the rabbit ureter and modeling of ureteral defects. (F) Macroscopic appearance and H&E staining (Left x 40, right x 100) of ureteral PCL/SF stents cultured in vitro at day 1 and day 14 (G) H & E and Masson staining 7 weeks after ureteral stent transplantation in rabbits (× 40). Reproduced with permission [129]. Copyright Elsevier. Reproduced with permission [130]. Copyright Turkish Association of Urology.

nephrotoxicity, and study early renal development. Organoids offer several advantages over traditional cellular and animal models, including bypassing ethical concerns in clinical research. They closely resemble the source organ, maintain genetic stability, and exhibit physiological and pathological characteristics similar to the human system. These benefits make organoids a valuable asset in ongoing research efforts.

Despite significant advances in recent decades, renal tissue engineering remains in its developmental stage. The technology still faces challenges in achieving complete reconstruction of engineered kidneys in vitro for transplantation through tissue engineering methods [14]. Therefore, continued selection and optimization of cells, scaffolding

materials, and culture environments are critical for the successful production of engineered kidneys in future studies. These efforts aim to create engineered kidneys with functionality that more closely mimics that of native kidneys, thereby enhancing their potential for transplantation. In the context of organ-on-a-chip technology, microfluidic systems , and kidney-on-a-chip models are utilized to replicate the kidney's microenvironment and hydrodynamic conditions. These platforms not only serve as valuable tools for investigating renal physiology and pathology but also play a pivotal role in drug screening and toxicity testing. To overcome the challenges of kidney tissue engineering, it is essential to integrate expertise from biomedical engineering, materials science, cell biology, and clinical medicine.

4.4. Ureter

Reconstructive surgery presents a complex urological challenge in the treatment of various pathological conditions of the ureter, including strictures, occlusions, and fistulas. While techniques such as ureteral stenting and percutaneous nephrolithotomy can address some cases of ureteral stricture, tissue grafts are often required for the repair of certain

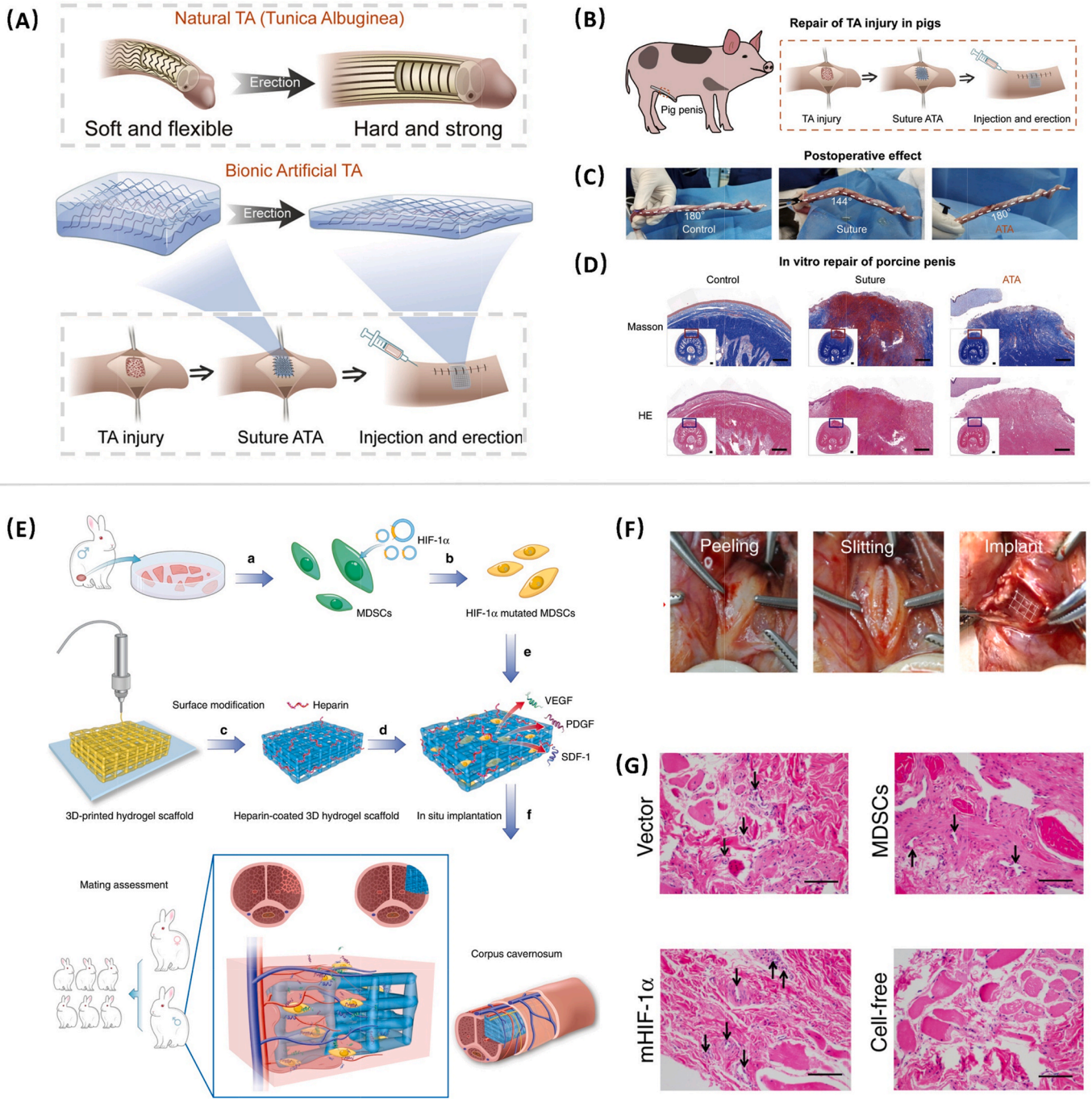

Fig. 24. (A) Diagram illustrating changes in the microstructure of TA during penile erection and the application of ATA in the repair of TA damage. (B) Diagram of the construction and repair procedure of TA damaged pig penis. (C) Postoperative penile erectile state of pigs. (D) H&E and Masson staining were used to evaluate the repair of TA injury 1 month after surgery. (Scale bar:500 μm) (E) Diagram of repairing damaged erectile tissue. (F) Surgical methods for repairing the damage of cavernous body. (G) H & E staining images of repaired cavernous bodies in each experimental group 4 months after transplantation. Reproduced with permission [6]. Copyright Elsevier. Reproduced with permission [136]. Copyright.

instances of ureteral stenosis, particularly when long segments are involved. Additionally, the surgical reconstruction of the ureter is further complicated by specific anatomical constraints, such as the segmental vascular supply [127]. Tissue engineering provides a novel therapeutic approach to ureteral reconstruction, aiming to improve outcomes in complex cases [128]. Several autologous patch materials are currently used in clinical applications, including appendiceal and oral mucosal patches. However, these materials have inherent limitations, and the outcomes of such repairs still require optimization. In a recent study, Zhao et al. fabricated scaffolds using vascular extracellular matrix (VECM) and differentiated urothelial-derived stem cells (USCs), exploring the feasibility of ureteral tissue engineering in a rabbit model (Fig. 23A). The results demonstrated that the microporous structure of VECM exhibited excellent compatibility with the seeded cells. Two months post-ureteral reconstruction, histological analysis revealed a well-formed laminar structure of the ureter, characterized by multiple layers of uroepithelium over smooth muscle tissue (Fig. 23B and C) [129].

In a physiological context, the ureter is continuously subjected to mechanical stresses and movements. If the mechanical strength of a tissue-engineered ureteral stent is inadequate, complications such as stent rupture or stripping may occur [131]. The ability to precisely control the lumen and wall thickness through electrospinning closely mimics the extracellular matrix, which promotes cell growth and tissue regeneration. This technique allows for the customization of scaffold size to meet specific clinical requirements. When combined with emerging technologies such as 3D printing, electrospinning has the potential to significantly improve the outcomes of ureteral reconstruction [132,133].

Hu et al. combined 3D bioprinting with electrospinning to fabricate PCL-sericin protein scaffolds with large pores (Fig. 23D and E). SEM and fluorescence staining showed that cultured 3T3 and SV-hUC-1 uroepithelial cells could selectively infiltrate polycaprolactone-silk fibronectin nanofibrous scaffolds within 3 days. The cells grew stably along the scaffolds for 2 weeks in ex vivo culture medium (Fig. 23F). In the animal model, after 7 weeks, different cellular layers were observed growing sequentially, including the outer mucosal, submucosal, muscular, and plasma layers of the scaffold. Notably, simultaneous growth of the mucosal and muscular layers was seen along the inner wall of the scaffold (Fig. 23G) [130]. This novel, 3D electrospun polycaprolactone-silk fibronectin nanofibrous scaffold demonstrates great potential for promoting tissue growth and ureteral reconstruction in animal models and shows promise as an alternative material for clinical urinary tract tissue repair.

The field of ureteral tissue engineering remains relatively underexplored, with limited published studies. However, recent advancements in cell sources, implantation techniques, and biomaterials have led to significant improvements. A series of animal studies, particularly in rabbit and canine models, have shown the promise of engineered ureters for repairing defects and restoring urinary function, demonstrating both feasibility and initial functional recovery with bioengineered ureteral stents. Small clinical trials assessing the safety and efficacy of engineered ureteral transplantation have yielded promising early results. Future research in ureteral tissue engineering should focus on overcoming vascularization challenges, which can be addressed by promoting neovascularization through the incorporation of angiogenic factors and optimizing stent design to ensure tissue survival and functionality. Additionally, investigating nerve regeneration is crucial for ensuring the full functionality of newly engineered tissues. A multidisciplinary approach, integrating techniques used in other urinary system tissues, is essential for accelerating clinical translation and evaluating long-term outcomes. Furthermore, exploring the mechanisms of cell-material interactions will provide deeper insights into this field. With continued multidisciplinary collaboration and technological advancements, ureteral tissue engineering holds great potential for developing safe and effective treatments for patients with ureteral defects, ultimately improving their quality of life.

4.5. Reproductive system

As a vital organ in the male reproductive system, the penis plays essential roles in both urinary and reproductive functions, including urination, spermatogenesis, and sexual intercourse. Tissue engineering offers significant potential for addressing various issues in the male reproductive system, such as injuries, congenital malformations, tumors, and sexual dysfunction [134,135]. Advances in tissue engineering technology have paved the way for new possibilities in penile reconstruction. However, the development of tissue-engineered penile constructs is still in its early stages. Successful organ reconstruction depends on the use of appropriate seed cells and degradable scaffolds. In a recent study, Chai et al. explored the creation of a bionic artificial penile tunica albuginea (ATA), which serves as a synthetic replacement for the natural tunica albuginea (Fig. 24A and B). ATA exhibits several key mechanical properties similar to those of the natural tunica, including rapid strain hardening in small deformation intervals, excellent fatigue resistance to withstand cyclic bursts, and high toughness to endure suturing. Moreover, ATA demonstrated the ability to repair damage and restore normal erectile function in tunica albuginea-injured penile tissue in a porcine model (Fig. 24C and D) [6]. Additionally, An et al. developed heparin-coated 3D-printed hydrogel scaffolds implanted with hypoxia-inducible factor-1α (HIF-1α)-mutated muscle-derived stem cells (MDSCs) to create bioengineered vascularized constructs (Fig. 24E). These HIF-1α-mutated MDSCs were capable of secreting a variety of angiogenic factors under both hypoxic and normoxic conditions. Upon implantation in a rabbit cavernous body defect model, the MDSCs exhibited excellent histocompatibility, no immune rejection, promoted tissue repair, and facilitated robust neovascularization (Fig. 24F and G). Functional assessments after repair showed that the bioengineered scaffolds effectively restored penile erection and ejaculation, ultimately leading to successful reproduction in subsequent trials [136]. Hydrogels, in particular, demonstrate great promise for repairing sponge-like tissue function due to their adjustable mechanical strength, multi-scale porous structure, and efficient drug-delivery capabilities [45,5].

Penile tissue engineering is a complex challenge due to the unique anatomical structure of the penis. The primary goal for urologists is to regenerate a normal, well-functioning penis that closely resembles the original in both appearance and function. Achieving optimal restorative outcomes requires a personalized treatment approach tailored to the specific needs of each patient. While there is still a gap in fully integrating tissue engineering within the reproductive system, it is expected to play an increasingly important role in future reconstructive therapies.

5. Recent advances in urinary system tissue engineering

The field of urinary system tissue engineering has witnessed transformative innovations aimed at overcoming the limitations of conventional surgical interventions. This section synthesizes state-of-the-art technologies, their mechanistic foundations, and clinical progress, with a focus on bladder regeneration, ureteral repair, urinary conduit reconstruction, and stress urinary incontinence (SUI) management.

5.1. Cell-free electroactive scaffolds for bladder regeneration

Electroactive biodegradable scaffolds, such as PEDOT-POCO composites, have emerged as a breakthrough for bladder regeneration. Keate, R. L. et al. report a functionalization method that confers electroactivity to a biodegradable elastic scaffold, facilitating the successful restoration of anatomical and physiological bladder function. By integrating conductive polymers with biodegradable substrates, the scaffold mimics native bladder electrophysiology, enabling cell-free regeneration. In vitro studies demonstrate that electrical stimulation enhances smooth muscle cell migration and alignment, while in vivo animal trials

confirm scaffold degradation and functional tissue restoration, including vascularization and muscle layer regeneration [137].

Challenges remain in optimizing electrical parameters for clinical use and ensuring long-term safety in large-scale models. This work underscores the transformative potential of electroactive biomaterials in urological reconstruction, integrating biodegradability, bioactivity, and streamlined application.

5.2. Autologous micrografting: Harnessing endogenous repair mechanisms

Autologous micrografting has emerged as a minimally invasive strategy for urinary conduit reconstruction, leveraging patients' own cells to bypass immune rejection. Urogenital reconstructive surgery is often limited by the insufficient availability of autologous tissue. Building on prior evidence that autologous micrografting enables single-stage scaffold cellularization, this study evaluated collagen-based scaffolds reinforced with biodegradable mesh and stents as bladder conduits in a porcine model. Ten female minipigs received either scaffolds embedded with perioperatively harvested autologous urothelial micrografts or acellular controls. After six weeks, assessments via cystoscopy, CT-urography, and histology revealed enhanced tissue regeneration in micrografted conduits, including improved luminal epithelialization, increased cellular proliferation, reduced apoptosis, and greater vascularization compared to controls. The procedure was surgically feasible, with operative times comparable to conventional techniques and no observed postoperative complications. All conduits remained patent post-implantation [138].

The key strength of this approach lies in its ability to harness the patient's own cells, thereby eliminating immune rejection risks and complications associated with synthetic materials (e.g., erosion or chronic inflammation). This technique holds particular promise for pediatric populations, where donor tissue scarcity and growth-related complications necessitate durable, adaptable solutions. Current research focuses on standardizing graft preparation protocols and integrating growth factors to accelerate vascularization.

5.3. Tissue-engineered therapies for stress urinary incontinence

SUI, a condition affecting over 200 million individuals globally, has witnessed remarkable progress through tissue engineering. MUVON Therapeutics has developed a tissue-engineered advanced therapy medicinal product for the treatment of SUI, utilizing autologous cells. This innovative approach is currently undergoing evaluation in a Phase II clinical study, representing a significant and challenging development endeavor [139].

Despite promising outcomes, scalability remains a major challenge due to the high costs of personalized cell expansion. Innovations such as automated bioreactor systems aim to standardize cell production, while combination therapies incorporating growth factors seek to accelerate functional recovery. Future trials will need to address long-term safety concerns and regulatory compliance to facilitate widespread clinical adoption.

5.4. Emerging frontiers and interdisciplinary synergy

The convergence of smart biomaterials and advanced fabrication techniques is driving the next wave of innovations. Stimuli-responsive hydrogels, capable of releasing therapeutics in response to physiological cues (e.g., pH or mechanical strain), are being tested for on-demand drug delivery during postoperative inflammation. Similarly, 3D bioprinting technologies enable the creation of patient-specific scaffolds with spatially controlled conductivity and degradation profiles, offering tailored solutions for complex ureteral or bladder defects.

Interdisciplinary collaboration is pivotal to overcoming persistent challenges. Engineers, clinicians, and regulatory bodies must collaborate to optimize manufacturing protocols, validate preclinical models, and harmonize safety standards. The integration of artificial intelligence for predictive scaffold design and robotic-assisted implantation techniques further underscores the transformative potential of this field.

The recent advances outlined herein highlight the paradigm shift toward biomimetic, patient-centric solutions for urinary system repair. While preclinical and early clinical data are promising, the path to widespread adoption requires addressing scalability, regulatory compliance, and long-term functional validation. By bridging gaps between laboratory innovation and clinical practice, tissue engineering holds the potential to redefine urological care, offering hope for millions of individuals affected by congenital, traumatic, or degenerative urinary disorders.

6. Conclusion

Tissue engineering holds immense promise in the field of urology, with the potential to revolutionize the treatment of a wide range of urinary and reproductive disorders. Although considerable progress has been made in mimicking the cellular structures and functions of natural tissues, several critical challenges remain to be addressed before tissue-engineered constructs can become the gold standard for clinical applications. These challenges include ensuring proper sterilization and preservation, managing immune and inflammatory responses, mitigating thrombosis and fibrosis associated with graft implantation, and addressing age-related factors that impact regenerative capacity in the human urinary tract. To overcome sterilization challenges, emerging strategies such as gamma irradiation-compatible biomaterial design and cryopreservation techniques incorporating ice-recrystallization inhibitors show potential for maintaining construct viability during long-term storage.

The integration of interdisciplinary research, combining expertise from materials science, cellular biology, bioengineering, and immunology, is essential to overcome these barriers. Recent advancements in 3D bioprinting with spatial control of bioactive factors enable precise recreation of urothelial-stromal interfaces, potentially reducing fibrotic encapsulation through anatomical mimicry. Stem cell therapies using urine-derived stem cells (UDSCs) offer autologous cell sources that maintain proliferative capacity even in elderly patients, addressing age-related regeneration limitations. The development of hybrid scaffolds incorporating anticoagulant heparin-mimicking polymers and endothelial progenitor cell recruitment motifs shows promise in preventing thrombosis while promoting graft vascularization. Furthermore, clinical trials and early-stage studies are beginning to demonstrate the feasibility of tissue-engineered constructs in urological applications, with nanoparticle-based contrast agents enabling real-time monitoring of graft remodeling through non-invasive imaging modalities.

Looking forward, the continued refinement of tissue-engineered solutions, particularly in terms of immune compatibility, vascularization, and functionality, will be pivotal in transforming urological care. Emerging approaches such as organ-on-chip systems for patient-specific drug testing and CRISPR-edited stem cells for genetic defect correction may enable personalized treatment paradigms. For vascularization challenges, microfluidic-assisted pre-vascularization strategies and oxygen-releasing biomaterials could enhance graft survival in hypoxic implantation sites. By overcoming these challenges through combination therapies that integrate biomaterial innovation, cellular engineering, and smart drug delivery systems, tissue engineering may ultimately provide more personalized, durable, and effective treatments for patients suffering from congenital defects, traumatic injuries, or age-related urological conditions. As the field continues to evolve, the convergence of artificial intelligence-driven scaffold design and robotic-assisted implantation techniques will likely play an increasingly central role in shaping the future of urological reconstructive surgery, offering hope for improved functional restoration and enhanced quality of life for affected patients. To ensure the safe and equitable translation of these innovations, global regulatory frameworks must adapt to address the

unique complexities of tissue-engineered products, including standardized validation of long-term biocompatibility, scalable manufacturing protocols, and ethical guidelines for genetically modified constructs. Collaborative efforts between regulatory agencies, industry stakeholders, and academic researchers will be essential to harmonize safety standards while fostering accelerated clinical adoption.

CRediT authorship contribution statement

Jie Yuan: Writing – review & editing, Writing – original draft, Conceptualization. **Di Suo:** Writing – review & editing, Writing – original draft, Conceptualization. **Penghui Li:** Writing – review & editing, Funding acquisition. **Xin Zhao:** Writing – review & editing, Supervision. **Huaiyu Wang:** Writing – review & editing, Funding acquisition. **Binghai Chen:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

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

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Data availability

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

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