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Reconstructive Urology and Tissue Engineering: Converging Developmental Paths

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Abstract

Reconstructive urology is a complex and demanding branch of modern urology. Complicated cases, necessity of microsurgical approach and constant exposure to urine make urinary reconstruction especially difficult. With impaired healing, excessive scarring and recurring fibrosis functional results are still not satisfying. For better, more successful outcomes a novel tissue engineering technology based solutions are being gradually investigated. The use of tissue engineering is the most promising strategy to improve results of reconstructive urology procedures due to possibility of designing organ- specific grafts. Moreover, targeted modification of healing environment by stem cells and growth factors is unique opportunity which might bring reconstructive urology on molecular level. Preclinical and clinical studies were conducted to evaluate feasibility and effectiveness of various in vitro crated grafts designed to replace diseased, resected or injured regions of urinary tracts. Research effort is specifically concentrated on three organs: urethra, urinary bladder and ureter. For each many biomaterials, and cell based therapies were tested. Results were highly encouraging however further advances and final translation into clinics require multidisciplinary approach.

Keywords: Tissue engineering; Reconstructive urology; Scaffold; Graft, Stem cells; Growth factors; Acellular matrix

Abbreviations: SIS: Small Intestine Submucosa; BAM: Bladder Acellular Matrix; BSM: Bladder Submucosa Matrix; UAM: Urethral Acellular Matrix; PLGA: Polylactide-Co-Glycolide; SMCs: Smooth Muscle Cells; NMIBS: Non-Muscle Invasive Cancer; MIBC: Muscle-Invasive Cancer; ECM: Extra Cellular Matrix; VEGF: Vascular Endothelial Growth Factor; FGF 2: Fibroblast Growth Factor 2; HB-EGF: Heparin-Binding Epidermal Growth Factor; PCL/PLLA: Poly(ε-caprolactone)/poly(l-lactic acid); CNS: Central Nervous System; MSC: Mesenchymal Stem Cells

Introduction

Modern reconstructive urology comprises of a range of surgical techniques developed to reroute, recreate, or repair damaged urinary tracts. General advances in surgery technology and the deeper understanding of urinary tract anatomy, and histology enabled the possibilities for rapid expansion of lower and upper urinary tract reconstructive modalities during the second half of the 20th century. The treatment of urethra strictures with clockmaker precision, new continent urinary diversions i.e., T-pouch, I-pouch, Studer-pouch or multimodal ureter reconstructions aim to guarantee low-pressure urine outflow with reduced risk of kidney dysfunction after long-term follow-up [1-3]. Restoring micturition functionality is, however, a partial therapeutic objective of reconstructive urology. Additional criteria such as the patients' quality of life, procedures' accessibility and invasiveness, and learning curve continue to develop until complete clinical potential is reached. In this context, reconstructive urology is slowly exhausting all possibilities for further development based on classical surgery techniques with roots from the 20th century. Therefore, it is high time to increase translation of tissue engineering technology, which opens up new frontiers and offers unique abilities to influence the course of urinary tract healing. Tissue engineering strategies utilising stem cells, biomaterial scaffolds or growth factor supplementation has the chance to make exciting new advances in reconstructive urology. Moreover, research at the interface of urology and regenerative medicine will lead to the development of a common interdisciplinary approach for future therapies that will combine surgery and biotechnology achievements.

Current Limitations of Reconstructive Urology

Advanced surgical techniques developed by reconstructive urologists aim to replace urinary tract wall of urethra, urinary bladder and ureter with similar material in terms of mechanical and biocompatibility properties [4]. Whenever there is a lack of native urologic tissues, reconstruction is usually performed using non-native urologic tissues i.e., gastrointestinal segments, skin, or mucosa from multiple body sites. For more than 100 years, intestinal wall has been the material of choice for urological surgeons struggling to reroute the normal flow of urine within urinary tracts on different levels [5]. The major advantage of intestinal wall is predisposed to tubularization and the ability to form differently shaped hollow reservoirs that structurally can compensate diseased or resected parts of urinary tracts. Additionally, intestinal wall is a well vascularised autologous material that does not carry the risk of extensive fibrosis or adverse reactions to biomaterials [6].

However, the composition of intestinal wall might be a reason for relevant complications when used in certain patients. Bowel segment removed for the reconstruction procedure retains its absorbing and

secreting functions that cause metabolic disorders during follow-up [7]. The principal metabolic abnormality in patients undergoing urinary tract reconstruction with intestinal wall is postoperative tendency for metabolic acidosis. Regulative mechanisms are often supported by pharmacological treatment to compensate for the unbalanced pH but Elderly patients are more predisposed to sever and rapidly occurring metabolic disturbances requiring hospitalisation [8]. Demographics of urological patients are shifting towards an increasingly elderly population, placing extraordinary pressure on urologists [9]. Since bladder cancer is an age-associated malignancy, surgical modalities must include the needs of the ageing population, thus minimising treatment-related toxicity and side effects. The concept of tissue engineering pursues the goal to limit invasiveness of the reconstructive procedure by delivering ready to use products designed for replacing the urinary tract wall.

Although sophisticated surgical techniques for urinary diversions, urethro- and ureteroplasty restore the proper function of urinary tracts, the reconstructed area might be at high risk for stricture formation due to the fibrosis [10]. This problem mainly concerns areas of small diameters between native and reconstructed regions as performed by anastomosis [11]. It has been shown that the glomerular filtration rate (GFR) decreases by 15–25% within 11 years after urinary diversion as a consequence of uretero-intestinal anastomosis stenosis [12]. Despite the introduction of several anastomotic techniques, none of them ensure long lasting results [13]. The extensive scarring is related to microtraumatization of the urethral and ureteric vascular plexus; that is difficult to omit or even recognise during surgery [14]. Subsequently, developing anoxia due to insufficient blood supply is responsible for surgical urethra (20%) and ureter (40%) repair failures.

Anoxia- triggered fibrotic reaction as evolutionary protective mechanisms aimed to rash isolation of injury site [15]. The healing process in an unfavourable environment ends in most of cases with severe scar formation [16]. The surgical techniques of reconstructive urology are slowly reaching their limit in terms of improving reliability and preventing scarring of urinary tracts. Even introduction of robotic surgery that enables better visualisation, high precision in suturing and manipulation didn't revolutionise the outcomes of reconstructive urology procedures [17]. Regenerative medicine composing of a wide range of tissue engineering methods allows for modification of the healing environment by supplementing growth factors or using bioactive scaffolds. Targeted modulation of the urinary tract healing mechanism might help prevent complications that result from insufficient natural healing where the dominant component is scarring instead of regeneration.

The functional outcome of reconstructive procedures within the urinary tract is dependent on the regeneration potential of anatomical and histological structures that are damaged by disease or during treatment. Continent orthotopic neobladder is the most sophisticated example of a modern reconstructive urology solution for urinary bladder replacement [18]. Nevertheless, the quality of life decreases for patients due to incontinence (up to 50%) [19]. The impaired ability of the sphincter to prevent urine leakage results from denervation and damaging the musculofascial spatial architecture of pelvic floor during surgery [20]. Nerve and urethral sphincter complex sparring strategies and reconstruction of musculofascial supportive systems don't guarantee proper continence [21].

Defined reconstructive urology challenges might be overcome with prompt translation of solutions from regenerative medicine that apply cutting edge research in tissue engineering (Figure 1A). This strategy efficiently compliments reconstructive urology surgery to enhance biomechanical results by focusing on induced regeneration (Figure 1B). Cell the subsequent constituted research platform between urologist and tissue engineer might result in pushing urology forward.

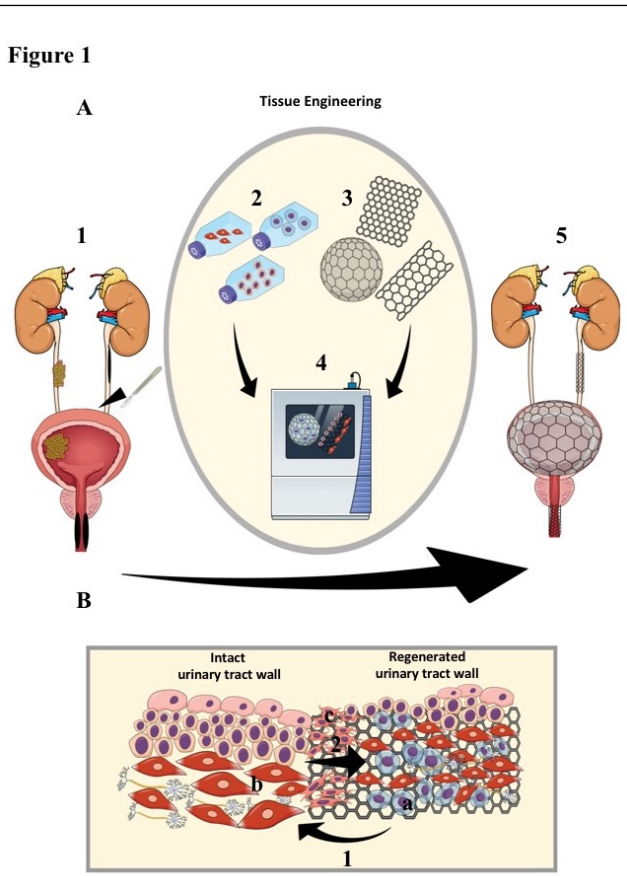

Figure 1: A. Tissue engineering based approach to urethra, urinary bladder and ureter regeneration.1) Major conditions requiring urinary tract reconstruction: malignancy, stenosis, iatrogenic injury and congenital abnormalities.2) Cellular strategy utilizing stem cells and autologous urothelial and muscle cells. 3) Biomaterial science offers plenty of differently shaped biomaterials of either natural or artificial origin that might be applied for future reconstructive procedures with implemented tissue engineering approach.4) Combining cells and biomaterial scaffolds allows crating *in vitro* grafts, typically generated prior to implantation in complex bioreactors simulating environment of urinary tracts. 5) *In vitro* crated grafts are design to replace instead of reconstruct urethra, urinary bladder or ureter. B. The concept of induced regeneration of urinary tract wall.1) Transplanted stem cells (A) are source of paracrine signals that activate intrinsic regeneration mechanisms in intact urethra, urinary bladder and ureter wall. 2) Urothelial, smooth muscle and neuronal cells (B) attracted by stimuli delivered by stem cells gradually migrate (C) into biomaterial scaffold and restore layered histological architecture of urinary tract wall.

Tissue Engineering Strategies for Urinary Tract Reconstruction

Urethra

Background: Urethral reconstruction is a challenging problem for modern urologists. The most common indication for such intervention is hypospadias among paediatric patients and urethral stricture among adults. Strictures can be caused by various medical conditions i.e., iatrogenic trauma, pelvic fracture, non-specific urethritis, lichen sclerosus and can be idiopathic. It is estimated that 0.1% of men above 65 will suffer from urethral stricture [22]. An estimated incidence of hypospadias is 0.7% in newborn male infants [23]. This indicates a substantial need for successful urethral reconstruction in modern medicine.

Positive clinical outcomes of the described intervention are based on a functional effect (proper urinary flow and ejaculation), minimal recurrence and complications rates, and minimal surgical side effects. In strictures longer than 1-2cm, or in complex cases, substitution urethroplasty is a preferred surgical solution that reconstructs a functional urethra with a proper diameter using a grafting material. Grafting can be used in partial repair (inlay/onlay technique) or in full circumferential reconstruction. Autologous buccal mucosa is the preferred material [24,25].

Urethral reconstruction using buccal mucosa is considered the gold standard with a success rate of +/- 86% [26]. Furthermore, harvesting buccal mucosa is associated with significant donor site morbidity; postoperative pain, numbness and tightness of the mouth, and changes in salivation. The rate of mentioned complications ranges from 16% to 32%. It is noted that complications may persist for more than a year after surgery [27]. Furthermore, the extent of material harvested from a patient's mouth is limited and in complex cases, may not be sufficient to substitute a long urethral stricture.

Tissue engineering based solution: Tissue engineering is a promising technique to overcome most of the mentioned obstacles in urethral reconstruction. In addition, a bioengineered graft can be produced without the need of additional surgery for the affected patient. This limits potential side effects associated with harvesting e.g. oral mucosa [28]. Another important advantage is the virtually unlimited quantity of biomaterial that can be transformed into a functional graft of any size. Furthermore, the beneficial function of growth factors is observed when stem cells and biomaterials are used together [29].

Various types of biomaterials were used either in experiments or in clinical practice; however, scaffolds from decellularised tissues are the most important. The first material that was broadly used in preclinical trials was small intestine submucosa (SIS). Most trials were based on non-seeded SIS scaffolds. Regenerated urethra consisted of differentiated epithelium, circular smooth muscle layers and connective tissue. Satisfying results were observed for partial reconstruction of urethra with a patch formed from SIS and implanted using onlay technique. However, for full circumferential substitutional urethroplasty, SIS has limited effectiveness when used without stem cell seeding [30,31].

Another promising material for urethral reconstruction is bladder acellular matrix (BAM) collected from porcine or leporine bladder. Multiple preclinical trials were conducted using BAM scaffolds with cell seeding and tubular scaffolds. Cells used were: autologous oral keratinocytes, adipose-derived stem cells, autologous bladder smooth muscle cells and urothelial cells [32-34]. An interesting biomaterial for substitutional urethroplasty was created by Chun, SY et al. [35]. The acellular bladder submucosa matrix (BSM) was combined with autologous urethral tissue. The scaffold was seeded with minced urethral tissue linked to BSM with fibrin glue. The experiment showed promising results when compared to reconstruction when BSM was used alone. The authors concluded that autologous tissue might increase graft incorporation and reduce risk of infection and rejection.

An organ-specific acellular matrix is another graft option for urethral reconstruction. In that case, the urethral acellular matrix (UAM) is a promising biomaterial. The tissue is collected from the donor, decellularised and the recipient's urethra is substituted by transplantation. The best results were observed when homologous transplantation was performed i.e., UAM produced from a donor rabbit's urethra was used to reconstruct urethra in a leporine model. Complete epithelialisation was achieved and smooth muscle bundles regenerated spontaneously [36]. Biomaterial seeded with autologous rabbit bladder smooth muscle cells and bone marrow derived mesenchymal stem cells were used in experimental trials and an organ-specific graft composing of allo/autologous components was constructed.

Synthetic matrices seeded with cells can also be used for urethral reconstruction. Various synthetic materials have been used, but the most important is polylactide-co-glycolide (PLGA). PLGA seeded with autologous bladder SMCs and urothelial cells was used by Raya-Rivera et al. [37]. There is also possible implementation of 3D bioprinting techniques using PLGA as a material.

There are many other biomaterials that have been used in basic and experimental research for urethral reconstruction, however, the most frequent and well documented are the ones discussed in this manuscript.

Challenges for future translation into the clinic: Besides numerous preclinical experiments, there are also some clinical trials for tissue-engineered grafts used in urethroplasty. Fiala et al. noted an 80% success rate in 50 operated patients using SIS without cell seeding [38]. A randomised controlled trial comparing BAM with oral mucosa was carried out by El Kassaby et al. displaying better results [39]. UAM has been used twice in clinical experiments with a success rate between 75-100% [40].

Translation of these techniques from basic experiments to clinical experience has numerous obstacles that need to be overcome. Data from preclinical trials is based on different animal models (rabbit, dog and rat) and various surgical modalities (full circumferential repair and substitutional urethroplasty with patch).

Legal regulation is a relevant problem concerning clinical application of cell-seeded biomaterials. The use of stem cells, even autologous, is associated with strict regulations and requirements that include the collection, storage, use and disposal of stem cells.

The current opinion of experts is the requirement for more unified basic research in terms of implementing tissue engineering in clinical practice for urethral reconstruction [41,42]. However, the presented technique is a promising option for future developments in regenerative medicine and reconstructive urology.

Urinary bladder

Background: Malignant and benign urinary bladder diseases may be an indicator for replacement. These include the management of

bladder cancer, neurogenic bladder conditions that threaten renal function, severe injury due to radiation, intractable incontinence in females, chronic pain syndromes, young patients with high-pressure, low compliant bladders due to congenital anomalies such as bladder exstrophy and myelomeningocele which, usually require augmentation cystoplasty at the early stage of treatment [43]. Bladder cancer is responsible for nearly 150 000 deaths worldwide each year and therefore represents a major indication for cystectomy. From a clinical point of view, the most important division is between non-muscle invasive cancer (NMIBC) and muscle-invasive cancer (MIBC) as these conditions require two different therapeutic approaches [44]. Bladder sparring strategies can also be applied in patients with NMIBC, however, MIBC requires radical cystectomy treatment; a challenging surgery with significant perioperative morbidity. Various methods are used for urinary diversion after radical cystectomy, such as ileal conduits, cutaneous continent urinary diversion and orthotopic neobladder reconstruction [45]. Despite the preferred method of urinary diversion, the patient's quality of life is affected postoperatively due to bothersome urinary leakage, creation of stoma, or distorted perception of body image [46].

Tissue engineering based solutions: In 2005, the milestone study of Atala et al. demonstrated the replacement of damaged urinary bladders using grafts constructed in vitro. Impressively, the authors obtained successful follow-ups [47]. The result of this study provided plausible evidence that an artificially created bladder composed from biomaterial seeded with cells might be an attractive substitute for a diseased bladder.

The bladder is a reservoir that stores and empties urine through a coordinated process that combines detrusor contraction or relaxation, and the passive mechanical properties of a bladder wall. The multilayered histological structure including the urothelial and smooth muscle layer guarantees proper bladder function. After years of research, two major tissue engineering based approaches to induced bladder regeneration were established; the use of acellular and cellular scaffolds [48]. The acellular scaffolds comprise of natural or synthetic biomaterials directed to activate regeneration mechanisms within the native bladder wall. The scaffolds also act as a temporary ECM for the arising urothelial and smooth muscle cells from the surrounding native tissue [49]. The acellular scaffold should simultaneously guide restoration of the bladder wall cytoarchitecture and prevent disruptive scarring. One of the major advantages of the acellular strategy is facilitation of in vitro graft construction and augmentation procedure, which don't require a transplantable cellular component. Following this concept, off-the-shelf products should be ready for instant bladder augmentation. Roefels et al. has recently demonstrated outcomes of porcine bladder regeneration using an acellular collagen scaffold enriched with heparin, combined with vascular endothelial growth factor (VEGF), fibroblast growth factor 2 (FGF2) and heparin-binding epidermal growth factor (HB-EGF) [50]. Histologically, after successful follow-up the neobladder wall was almost indistinguishable from a native one containing a well-developed layered structure. Nevertheless, the applied composition of growth factors failed to improve regeneration quality. In this regard, a decellularised scaffold such as BAM or SIS with naturally incorporated active factors within the ECM had a better ability to induce regeneration [51]. Therefore, it is important to recognise the various signalling pathways regulating specific stages of regeneration. Elucidation of the signalling pathways would allow for predicting the mechanism of action for scaffolds enriched with artificial growth factors, thus controlling the process of induced regeneration. The current understanding of cellular communication doesn't allow for precise regulation of regeneration events; hence natural bioactive materials such as BAM, AM and SIS showed superior results. Using BAM as a biomaterial for tissue engineering is tempting since it opens up new perspectives such as whole bladder replacement. Furthermore, BAM preserves an organs shape during the decellularisation process and thus, maintains the original three-dimensional structure [52]. Use of BAM as a neobladder might allow for similar biomechanical properties, as a native bladder withstanding high tensile and repetitive stresses without plastic deformation or rupture. The interplay between the mechanical extracellular environment and the mechanical properties that characterise the dynamic intracellular environment is poorly understood. The application of BAM could be a vicarious solution until the understanding of the relationship between ECM composition and bladder biomechanics becomes clearer, which will allow for design of a scaffold with analogues properties to a normal bladder.

Electrospinning technology has emerged as a pivotal tool to construct novel scaffolds for bladder regeneration. It enables a wide range of biomaterial customisation according to biodegradability, mechanical resistance and compliance [53]. The potential of electrospinning for acquiring new scaffolds is attributed to adaptability and the ability to fabricate fibres with diameters in the order of some hundred nanometers. Scaffold engineering on the micro and nanoscale obtain topography and porosity similar to the natural extracellular matrix. Compared to the architecture of a native bladder tissue, synthetic electrospun scaffolds create favourable attachments for cell-to-substratum adhesion and cellular migration. Ajalloueian et al. optimised an electrospinning protocol to obtain a poly(lactic-co-glycolic acid) (PLGA) scaffold with a porosity adjusted to support neovascularisation and proliferation of cells from the bladder mucosa [54].

Shakhssalim et al. succeeded in applying electrospinning to generate PCL/PLLA scaffolds (10cm^2) for canine bladder wall replacement. Cellular matrices supported the maintenance of seeded detrusor smooth muscle cells, which *in vivo* stimulated the growth of local native cells [55]. Agrawal et al. indicated that electrospun nanofibers might provide "surface guidance" to control the orientation of elongating muscle bundles. Smooth muscle cells migrate longitudinally along PCL nanofibers and simultaneously acquire contractile phenotypes [56]. The guidance of regenerating detrusor muscle components would be of key significance for restoration of muscle layer topography, which determines the proper transmission of forces generated by the contraction of muscles during micturition.

A promising strategy is aimed at hybrid scaffold design for bladder tissue engineering. Joining features of biomaterials from different origins allows for complementation of characteristics and elimination of limitations linked using of only one particular biomaterial. This approach allows us to obtain a complex mechanical environment where parameters might be extensively customised. Horst et al. recently covered BAM with electrospun PLGA in order to obtain biomaterial comprising of unique polymeric microfibers traits and naturally derived acellular matrices [57]. The PLGA fibres enhanced BAM mechanical resistance and counteracted its susceptibility to shrinking. Thanks to the fabricated bilayered biomaterial, normal bladder capacity was maintained. A similar strategy was applied in our previous study to adopt AM for bladder augmentation using rats as our model [58]. Sandwiched structured biocomposite combined with electrospun PCLC excellently provided mechanical resistance with AM biocompatibility. The delicate AM ECM gained necessary structural

support and in turn, might be used for urinary bladder reconstruction without risking graft breakdown.

Major research efforts are focused on obtaining regenerated urinary bladders, but tissue engineering might offer a more plausible option. The first product obtained from the tissue engineering industry might be Translation of artificial urinary conduit biomaterial into reconstructive urology [59]. In this approach, the biomaterial's characteristic needs to mimic the biomechanics of the intestine wall and provide a suitable surface for urothelial and smooth muscle cells. Despite the unsuccessful translation of neo-urinary conduit ™ (Tengion) into clinics; this idea is still being developed [60]. The major obstacle, identified during research and developmental studies, was the difficulty to obtain effective vascularisation of the implanted conduit. The major advantage of artificial urinary biomaterial would be elimination of the necessity to open the gastrointestinal tract and detubularisation of the bowel segment. This is recognised as a major factor in determining high complication rates, especially in older patients. Tissue engineered urinary conduit would convert the demanding multi-stage ileal conduit surgery in such a way that the commercial graft only needs ureter anastomosis and urostomy formation. Without the need for bowel segment tubularization, facilitation of intracorporeal laparoscopic and robotic urinary diversion surgery may occur.

Challenges for future translation into the clinic: Considered to be the flagship goal of tissue engineering is the development of urinary bladder regeneration technology. A major concern is the lack of published data from studies using large animal models that poses a high translational potential [61]. There is an urgent need to collect more reliable, high quality data to plan clinical trials and to define a consistent path for further development. Unrecognised adverse effects during experimental urinary bladder reconstruction might put patients in danger and discourage urologists to follow this concept. Previously, severe complications led to premature termination of clinical trials evaluating promising biomaterials for bladder cystoplasty [62].

Urinary bladder compliance is a result of passive bladder wall elasticity mainly corresponding to ECM biomechanics and smooth muscle tension regulated by the nervous system [63]. Current biotechnology struggles to provide tools for simultaneously enhancing the regeneration of all histological components and building a bladder wall. The main research effort is, however, focused on smooth muscle and urothelial layer regeneration, whereas reconstitution of the neural network has been neglected. The bladder neural plexus fails to regenerate beyond the lesion site and native axons don't elongate into the tissue-engineered graft [64]. In this context, rebuilding the neural network within the neobladder wall should be a high priority. This might be achieved by stimulating the regeneration of neural cells per so or replacing them with an electroactive biomaterial that mimicks the bladder neural network. In a second step, the integration of the neobladder with the host peripheral and central nervous system (CNS) must be addressed. The most tempting idea is to design a biochip that would regulate bladder function by combining CNS signalling with tissue engineered peripheral regulating pathways.

Tissue engineering strategies that are currently being pursued offer the ability for partial bladder augmentation [65]. This is a good entry point into clinics, but considering the needs of the urologist, the indications for partial bladder reconstruction are limited. Most patients require total bladder replacement after cystectomy and in these circumstances tissue engineering needs to target this population as a major group awaiting novel treatment modalities.

The wall of urinary bladder has a heterogenous histological structure, dependent from anatomical localisation and physiological function [66]. Thus, the next step should address the regeneration or replacement of defined bladder regions such as the trigone or doom, taking the structural and functional differences into account. Recent advances in the field of 3D bioprinting made it possible to arrange cells and scaffold components into complex 3D neotissues, which might be applied for this purpose.

Ureter

Background: Iatrogenic injuries contributed to the largest number of damaged ureters that require sophisticated urological treatment. The ureters are usually injured in gynaecologic, colorectal, and vascular pelvic surgery [67]. About 70% of ureteral injuries occur during gynaecologic procedures [68]. Latent mucosal abrasions after endoscopic procedures (core to modern urological treatment) might end with local scarring and obliteration of ureter lumen. Incidental ureter ruptures during endoscopic treatment or intentional partial resections due to cancer remain challenging situations in urology and concern many patients [69].

Devised surgical techniques aim to create favourable anatomical situations to reconnect the bladder to the ureter i.e., the psoas hitch, the Boari flap and the downward mobilisation of the respective kidneys is followed by high complication rates and anastomosis site strictures [70]. In general, 3–5 cm of ureteral length can be gained with this approach. If ureteric repair remains impossible by bladder bridging techniques, intestinal ureter substitution does remain as an option. From a clinical point of view, the new modalities for full-circumference long ureteral defect repair are of great importance [71].

Tissue engineering based solution: The field of ureter regeneration with a tissue engineering approach seems to be a neglected area of research in comparison to experimental bladder and urethra regeneration. Advances in ureteral replacement are technically hampered by demanding animal models requiring microsurgery. Different natural biomaterials like SIS, decellularised ureter, vessels or synthetic ones like Gore-Tex (polytetrafluoroethylene) were tested as scaffolds for induction of ureter regeneration [72]. Regardless, all these experiments failed due to complications or segment reconstruction not being significantly long enough.

One of the first successful restorations of the ureteral lumen and wall was demonstrated clinically by Davis in 1943 [73]. This was achieved by incision and stenting of a ureteral stricture. Hinman et al. formulated a guide for ureteral regeneration, which underlined the necessity of restoring the smooth muscle layer continuity in order to prevent scaring and preserve peristaltic waves [74]. A tissue-engineered ureter must have ongoing flexibility and patency shortly after implantation, and continuing indefinitely thereafter. Versteegden et al. fabricated a collagen-based tubular scaffold that possesses intrinsic radial elasticity [75]. The scaffolds lumen opens upon the increase of pressure with passing fluid. The combined characteristic of this scaffold with the regenerated smooth muscle layer might be ideal for restoring neo-ureter behaviour and in turn, effective urine passage.

Available data shows that short defects revealed limited self-regeneration potential supported by scaffolds without preseeded cells *in vivo* [76]. Due to diameter compatibility, many studies evaluated tissue engineered blood vessels [77,78]. The intrinsic ECM ultrastructure and collagen composition of arteries is similar to the ureter ECM, and should thus create an adequate microenvironment for

the cellular component of the ureter wall. Kloskowski et al. compered the regenerative outcomes of a synthetic scaffold *vs.* a naturally derived aortic arc obtained from a rat model. Both acellular matrices failed to uninterruptedly restore smooth muscle membrane [79]. Only limited focal regrowth was reported after 4 weeks follow-up. Although studies carried out in small animal models showed potential to regenerate ureter without cell transplantation, analogous approaches in large animal models led to extensive scarring and fibrosis after stent removal within the retroperitoneal space. Engel et al. bridged ureter with autologous venous graft and reported after 6 months follow-up missing smooth muscle and urothelial cell layers within the reconstructed segment [80]. Proper urothelium was confirmed only in grafts pre-seeded with urothelial cells. The healing environment of ureter is demanding because of insufficient local blood supply after injury. Anatomically regionalised ureter vascular bed with limited linear anastomosis is prone to disruption. Reoccurring reports of extensive fibrosis underlined the necessity to develop cell-based strategies in order to bridge long ureter defects [81,82].

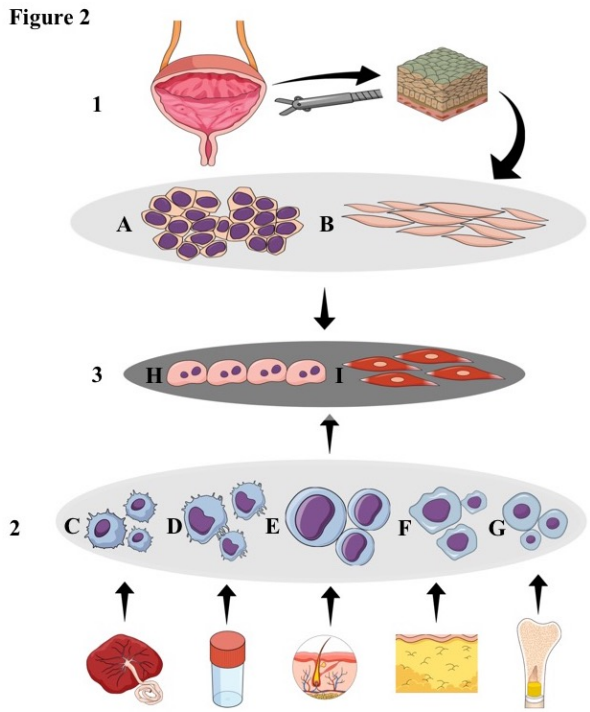

Figure 2: Established cell sources for urological tissue engineering. 1) Progenitor urothelial (A) and smooth muscle (B) cells might be isolated for urinary tract wall. Future isolation protocol should ideally enable to obtain enough cells from forceps biopsy. 2) Stem cells derived from different sources with differentiation potential into urothelial and smooth muscle cells: (C- Amniotic fluid/ membrane stem cells), (D- Urine derived stem cells), (E- Hair follicle stem cells), (F- Adipose tissue derived stem cells), (G- Bone marrow derived mesenchymal stem cells).3) Obtained mature, ready to be seeded on biomaterial scaffold urothelial (H) and smooth muscle (I) cells capable to reconstitute urothelial and smooth muscle layer of tissue engineered urinary tract wall.

Koch et al. proposed the use of decellularised and cross-linked ureters from porcine donors as regenerating scaffolds for the human ureterine wall [83]. Within two weeks, the seeded smooth muscle cells uniformly populated the scaffold making the graft ready for ureter bridging. Liao et al. created ureteral grafts from BAM seeded with MSC and smooth muscle cells using a rabbit model [84]. After 16 weeks, well-organised and aligned smooth muscle bundles were described within the entire grafts length. In order to improve regeneration results, Zhao et al. proposed to employ blood vessel ECM seeded with MSC to bridge long ureteral gaps [85]. The authors postulated that the obtained multilayered ureteral tissue originated from differentiated MSC. Urothelium positively expressed cytokeratin 20 and uroplakin III over connective smooth muscle tissue stained with a-SMA and SM-MHC (Figure 2).

Local ischemia was recognised as a major factor for hampering ureter regeneration. This conclusion led to the development of a two-step ureter graft replacement technique allowing for vascular plexus development. Initially, the constructed graft was temporarily implanted into the omentum to create an *in vivo* vascular pedicle additionally incorporated with the tested scaffold [79]. Subsequently, vascularised material was ready to be shifted to bridge the ureter defect. Favourable ureter anatomical localisation facilitating surgical access and intraoperative manipulation might accelerate translation of this strategy into clinics.

Challenges for future translation into the clinic: Restoring the ureters motility should gain attention to guarantee low-pressure urine transport. This crucial aspect of ureter tissue engineering tends to be neglected in experimental settings. The neo-ureter needs to propagate contraction waves pushing the urine bolus downwards into the bladder. This is particularly important during attempts to connect cut ends of the middle ureter. At this level, the urine flow is mainly dependent on peristaltic force generated by the ureter. Acontractile ureteric wall significantly impairs urine flow even by unobstructed lumen [86].

The unicalyceal rodent kidneys, in comparison to other mammals, vary in terms of pyeloureteral motility and ureteral peristalsis [87]. This implicates that physiologically quiescent rodent ureters aren't adequate as experimental models to test ureteral peristalsis. Moreover, the outcomes of experimental ureter regeneration were evaluated based on grading hydronephrosis that developed postoperatively. Novel urine biomarkers for obstructive nephropathy that precede hydronephrosis might be used for more precise monitoring of urine outflow in reconstructed upper urinary tracts [88].

Advanced tissue engineering therapies utilize transplantation of living cells and hence constitute one of the most labyrinthine, in terms of organization and law regulations, field of medicine. Tissue engineered products manufactured from autologous, allogeneic or xenogeneic cells combined with biomaterials or different chemical/ biological components are qualified as Cell-based Medicinal Products (CBMPs) or Advanced Therapy Products (ATPs) [89]. Their production and distribution are authorized through central agencies enforcing strict compliance with c-GMP (current Good Manufacturing Practices) protocols. The European Union institutions agreed on a regulation on advanced therapies coordinated by European Medicines Agency [90]. Analogously, in the USA, the Center for Biologics Evaluation and Research (CBER) regulates cellular and biomaterial based therapies [91]. A regulatory framework is indeed necessary to ensure patients' safety but on the other hand academic scientists and clinicians may feel overwhelmed by the apparently endless regulatory

requirements. In this situation, the governmental assistance should also include research staff trying to implement tissue engineering therapies into urology and other medical disciplines. As the principals of tissue engineering are universal more efforts should be also undertaken to unify the regulatory aspects of tissue engineering translational research worldwide.

The bulk of indications for urinary tract reconstruction with tissue engineering strategy would be due to radical oncological treatment. This scenario limits the usability of autologous cells derived from host urinary tract as they are at risk of carcinogenesis [65]. Allogenic transplantation of progenitor urothelial and smooth muscle cells might be adequate solution however this approach has never been sufficiently researched on large animal model. To avoid stagnancy, we must start to plan integrative studies answering questions raised by transplantologist or immunologist, with priority placed on establishing specific cell typing protocols. Allogenic cell transplantations have been successfully developed in oncological hematology since the 1960s and hence might provide helpful basis for transplantation of cells harvested from urinary tract wall [92]. In context of this speculative paragraph, the existing infrastructure designed for hematopoietic stem cell transplantation might be even applied in urology for tissue engineering purposes.

Summary

Considering all the mentioned techniques and modalities, tissue engineering seems like a natural path for the development of reconstructive urology. A Rapidly ageing population will increase a substantial need for urological instrumentation, endoscopic diagnostics and invasive curative procedures, and an in increased need for reconstructive surgeries in complicated cases, and the substitution of resected organs.

Furthermore, an important outcome of successful management in urology is a good quality of life. In that case, a satisfying functional effect (defined as proper urine flow, continence and low recurrence rate) is a key to understanding the need for further improvement in reconstructive urology. Using examples described above, we can conclude that tissue engineering may potentially overcome the most important obstacles in reconstructive urology e.g. scarring of reconstructed tissue and insufficient amounts of tissue for autologous reconstruction. However, potential positive effects of regenerative techniques are now diminished by high costs and lack of high- quality clinical data. The Cost-effectiveness of tissue engineering will probably improve after adoption of that technique. Involvement of industry and financing may help improve technical aspects, and facilitate large-scale production of scaffolds and biomaterials.

At present, more preclinical and clinical results are required to boost successful implementation of tissue engineering in everyday clinical practice. That may be achieved by establishing dedicated working groups with clinicians and biotechnologists that aim to overcome any obstacle. In that setting, clinical needs presented and clearly defined by an urologist can be resolved technically by a biotechnologist. These groups can also conduct trials (preclinical and clinical) in an effective way, based on simultaneous, continuous and day-to-day cooperation.

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