Renal tissue engineering for regenerative medicine using polymers and hydrogels

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Chronic Kidney Disease (CKD) is a growing worldwide problem, leading to end-stage renal disease (ESRD). Current treatments for ESRD include haemodialysis and kidney transplantation, but both are deemed inadequate since haemodialysis does not address all other kidney functions, and there is a shortage of suitable donor organs for transplantation. Research in kidney tissue engineering has been initiated to take a regenerative medicine approach as a potential treatment alternative, either to develop effective cell therapy for reconstruction or engineer a functioning bioartificial kidney. Currently, renal tissue engineering encompasses various materials, mainly polymers and hydrogels, which have been chosen to recreate the sophisticated kidney architecture. It is essential to address the chemical and mechanical aspects of the materials to ensure they can support cell development to restore functionality and feasibility. This paper reviews the types of polymers and hydrogels that have been used in kidney tissue engineering applications, both natural and synthetic, focusing on the processing and formulation used in creating bioactive substrates and how these biomaterials affect the cell biology of the kidney cells used.

Introduction

About 10% of the world’s population is affected by kidney diseases.1 It is considered a global burden by World Health Organisation, with 5–10 million deaths estimated annually due to this condition.2 Kidney failure or end-stage renal disease (ESRD) occurs when chronic kidney disease reaches an advanced state with the kidney having less than 15% of its function.

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usual efficiency both as a crucial excretory organ to filter the blood and in maintaining the homeostatic balance in humans. The most common causes that lead to kidney failure are diabetes and high blood pressure. ESRD is categorised into two major groups, acute kidney diseases and chronic kidney diseases.

Acute kidney disease (AKD) or acute kidney injury (AKI) is defined as the rapid deterioration of kidney functionality, usually within hours, which involves structural damage and loss of functionality. These conditions are incurred abruptly, typically due to a physical blow during an accident, by a severe infection or sepsis, or ischemia; restriction of blood supply to carry oxygen to tissues, and kidney reperfusion that causes tissue injury. Besides that, autoimmune diseases may also contribute to this type of kidney failure, such as systemic lupus erythematosus, when autoimmune antibodies attack body tissues, and vasculitis, when the immune system attacks small vessels within the kidney, and diabetes, caused by metabolic changes due to hyperglycaemia. There are several other causes, including autoimmune disease such as lupus nephritis, a congenital condition such as polycystic kidney disease, a state where the kidney contains multiple fluid-filled cysts, neuropathy such as diabetic and obstructive nephropathy, and also urinary tract condition such as reflux nephropathy, a condition where kidney scarring happens due to urine backflow from the bladder towards the kidney, which can cause CKD. These conditions damage the kidney, initially affecting filtration efficiency and, eventually, its overall functionality, both mechanically and physiologically.

This article reviews current treatment options for kidney diseases and explores the progress made in engineering kidney tissue. The current treatment for CKD and ESRD has been briefly described. Then, the need for kidney tissue engineering for regenerative medicine purposes is emphasised along with current strategies that have been used. The article continues with a detailed review of materials, specifically polymers and hydrogels, both synthetic and natural, used in exploring their compatibility with kidney cell culture. The content primarily focuses on using biomaterials in research efforts and strategies to develop functional kidney tissues by utilising these materials through fabrication and modification. This review will shed light on the advancements and challenges in creating functional kidney tissues for potential therapeutic interventions by examining these biomaterials, their properties, and their applications in kidney tissue engineering.

Current treatment for CKD and ESRD

Current treatment options for ESRD are inadequate as there is a lack of suitable donor organs for transplantation, and conventional haemodialysis acts merely as a filter without replacing the normal physiological, metabolic, endocrine and regulatory functions of the kidney. Hence, novel treatment approaches are urgently required. There is increasing interest worldwide in developing a bioartificial kidney using tissue engineering. This is a difficult problem since the kidney is a complex organ and consists of at least 26 types of cells operating in a single system.

Haemofiltration by dialysis

There are two well-known approaches to addressing CKD and ESRD. One approach is dialysis, an artificial way of undergoing haemofiltration that the diseased kidney lacks. This method was invented by a Dutch physician, Willem Johan Kolff, in the 1940s using a tank equipped with cellulose membrane and tubing that allows blood to flow out of the patient's body into the haemofiltration unit. The Kolff-Brigham dialyser uses the osmosis principle to diffuse the waste and excess fluid across the membrane into the dialysate. His dialyser prototype pioneered the modern dialysis machine. Peritoneal dialysis is
another type of dialysis that relies on the abdominal lining, *i.e.* the patient’s peritoneum to perform haemofiltration. A dialysate is introduced within the peritoneal cavity, allowing excess fluid and waste from the blood vessels to pass through the peritoneal membrane by diffusion.21 The dialysate is later drained and replaced with a fresh one.

Dialysis is the main and much accessible treatment that has been used worldwide since kidney failure affects millions of people worldwide. According to the United States Renal Data System (USRDS) 2020 Annual Data Report, more than 500 000 people in the United States and 2.6 million worldwide undergo dialysis per annum.22 Therefore, kidney failure is very common; and because of this, dialysis is also common and deemed as a conducive treatment. However, it does not improve the quality of life of a patient. They need to be attached to the dialyser for a standard four-hour session frequently, through a surgically made arteriovenous fistula, up to four times a week.

Dialysis is also very expensive and requires several types of drugs to balance some dialysis-induced conditions. One of the common drugs used is an erythropoiesis-stimulating agent to address anaemic episodes among diabetic patients and allow the formation of new blood cells.23 Hypertension is also common among the patients, and medication such as angiotensin-converting enzyme (ACE) inhibitor, angiotensin II receptor blockers (ARBs), beta-blockers and calcium channel blockers help to decrease complications such as heart conditions.24 Other supplements, help in alleviating deficiencies such as iron and vitamin D, while a phosphate binder reduces phosphate in the blood due to ineffective phosphate elimination by the impaired kidney.

**Kidney transplantation**

Kidney transplantation is another treatment for CKD and ESRD, mainly for patients suffering from glomerulonephritis, diabetic nephropathy and polycystic kidney disease.11 The procedure introduces a healthy kidney into a patient, surgically, to replace the diseased one. The first ever successful human kidney transplant was done by Dr Richard Lawler in Illinois, USA, on a lady with polycystic kidney disease.12 Through the procedure, a healthy and functional kidney is harvested from a living donor or a deceased donor and transplanted into the patient.

Although this procedure is ideal in significantly improving the quality of life for the patient with kidney failure, the major hurdle is finding a suitable donor. In fortunate cases, the patient might have a donor among family members willing to donate one of the pairs and is physiologically compatible. Otherwise, the patient must be on an extraordinarily long waiting list to get an organ from a deceased donor. The challenge continues as the patient needs immunosuppressive agents such as calcineurin inhibitors, antiproliferative agents that suppress immune cells, and corticosteroids to reduce inflammation. Some of them might need to start a diabetic medication regime for new-onset diabetes after transplantation or NODAT, or even those with diabetes pre-transplantation.25 Given that some patients are not accustomed to a healthy lifestyle, they are prone to relapse and face the risk of failure of the transplanted kidney.

The available treatments for kidney failure, which are haemodialysis and kidney transplantation, provide an option to manage renal patients. While they have proven to prolong life expectancy, their effectiveness and feasibility may vary across individuals. Therefore, personalised approaches are necessary since the needs of each patient needs are different.

**Kidney tissue engineering**

Tissue engineering research provides the opportunity to mimic organs and potentially develop fully functional organs to replace diseased or damaged ones. A suitable material that serves as a biological substrate is vital to promote the required cell proliferation, maintenance, and maturation, to allow functional tissues to develop at the cellular level. There are three aspects of kidney functionality that need to be addressed in any model, specifically in kidney tissue engineering; haemofiltration (glomerular cells), reabsorption of water (tubule cells) and metabolic and endocrine activities (interstitial cells).18

Organ shortage is the main reason of why transplantation is not usually an option in the event of organ failure, including the kidney. Tissue engineering strives to address this problem by developing an improved treatment option. Since tissue engineering is a type of personalised medicine, this approach would reduce the risk complication and be less heavily dependent on medication by considering patient’s immunological and physiological need, case by case.26 Also, tissue engineering offers a step forward in developing an advanced diagnostic tool to detect disease in patients without major intervention, in the form of *in vitro* organ models. Again, the diagnosis can be tailored to a specific patient’s condition and generate results for precise treatment regimes.

Kidney tissue engineering has been attracting major attention and in multiple ways, scientists are attempting to recreate a functional kidney. Since it is a relatively new area, it is important to understand (1) the cellular biology of kidney cells and potential materials that may support the growth of kidney tissue; (2) the selection of suitable biomaterials is crucial, especially with respect to biocompatibility, *i.e.* the lack of any adverse effects that hinder development of functional tissue; and (3) the fabrication of the biomaterial should be precise in order to facilitate tissue engineering in three-dimensional scaffolds to imitate the native structure of cell organisation in the kidney. Other methods, such as enhanced biocompatibility induced by material modification and creation of a drug release system, provide added value to the engineered scaffold.

The materials most frequently used in kidney tissue engineering are polymers and hydrogels. Polymers are known for their processability to replicate kidney features in terms of mechanical properties. In addition, polymers can be blended with bioactive components such as an extracellular matrix and growth factors that would in turn enhance the bioactivity of the polymer.27,28 Hydrogels, on the other hand, are widely
used to imitate the extracellular matrix in vivo, as well as carriers for the cells, and are commonly used in cell therapy approaches. Furthermore, polymers and hydrogels are very robust and amenable to majority of the material processing techniques, for example, 3D printing and electrospinning for shape-tailored scaffolds, salt-leaching for introducing porosity in polymers,\textsuperscript{28} polymer emulsification method to control the size of cells encapsulation, and development of bioinks for spatially controlled cell culture using 3D printing of hydrogels.\textsuperscript{29}

**Brief overview of kidney tissue engineering: strategies and application**

Several attempts at kidney regeneration have been undertaken using allotransplantation of kidney components with the goal of restoring the original functionality of the kidney. Current work is mainly based on small animal models, i.e., rats and mice. Even though the animal study may not be considered a perfect representative of human physiological makeup, especially by direct comparison to the human kidney's complexity, it serves as a preliminary tool in shedding light on certain biological mechanisms, in addition to gaining validation through proof-of-concept experiments. Some approaches include the implantation of embryonic nephrons into the kidney, implantation of nephros beneath the renal capsule, in situ kidney regeneration, utilisation of stem cells and bioengineering of an artificial kidney.\textsuperscript{18}

**Allograft of kidney tissue**

Starting with the allograft approach, researchers introduced foetal renal tissue into a specified location, such as the renal capsule.\textsuperscript{30–33} However, this approach is only partially sustainable, with rejection in most cases. One set of studies focused on metanephrons, a type of renal tissue that is in the early structures involved in kidney development in an embryo. In murine models, allogenic grafts of embryonic metanephrons were transplanted into the anterior eye chamber and the renal capsule within the renal cortex, as a proof-of-concept study. These grafts showed high vascularity and the formation of new nephrons. Also, glomerular and tubular cells in the graft exhibited cytodifferentiation. However, graft rejection occurred after approximately 16 days.\textsuperscript{30} Another approach involved the allograft of adult and foetal renal tissue beneath the murine renal capsule. The adult renal tissue experienced rejection after 10 days, while the foetal renal tissue demonstrated growth, neovascularization, and limited signs of rejection after 10 days.\textsuperscript{31} In a different study, renal tissue derived from foetal midgestational tissue grafts were placed beneath the renal capsule. It was observed that the graft had a prolonged survival due to the lack of major histocompatibility complex or MHC, class I and II mRNA production. Furthermore, the transplantation of human foetal renal tissue revealed that the immune response leading to kidney rejection was dependent on the cell source, with foetal grafts exhibiting a favourable allogenic response for implantation.\textsuperscript{32,33}

On the other hand, an extraordinary attempt with a chimeric animal model approach involving kidneys from murine and avian sources observed the development of glomeruli and tubules, which extended to the medulla of the kidney after transplantation.\textsuperscript{34} In another study a similar approach was adopted, utilising gelatine microspheres as a cell carrier for rat kidney tubular cells in a cellular therapy approach. Some neo-vascularisations had occurred that may promote the development of healthy kidney structure.\textsuperscript{35}

In summary, the tissue engineering approach involving the implantation of early-stage kidney tissue derived from an embryo was deemed feasible in repairing damage in the injured kidney. This tissue possess a greater capacity for proliferation and differentiation ability due to the availability of progenitors that can condition themselves in the new environment. This is crucial in developing fully functional and properly organised tissue. In contrast, the readily developed and differentiated adult kidney tissue may not properly adapt and thrive to give rise to a functional tissue; hence the chance of rejection is high. However, further optimisation still needs to be carried out since the goal is to enable essential functions of the kidney, especially haemofiltration and water reabsorption. The studies are summarised in Table 1.

**Development of bioartificial kidney**

The main aim of developing a bioartificial kidney is to address shortages in artificial kidneys. Bioartificial kidneys work with the incorporation of renal cells within an engineered artificial construct, which would extend the device's functionality with the presence of metabolically active components. Since the kidney's primary function is to filter blood, hence, the focus is to create a bioartificial filtration barrier that can mimic in vivo haemofiltration mechanism. The tissue engineering strategy for this objective is to create a confluent monolayer of kidney cells on a support material. Then, the cell-scaffold hybrid will serve as a filtering membrane while sustaining cellular growth over time.

The emphasis of the bioartificial kidney is the presence of living cells within the construct. Hence, their metabolic activities are the key focus in ensuring optimum performance and determining the feasibility of the artificial environment. In renal epithelium, for instance, metabolic activities such as ammoniagenesis; a way to excrete excess acids, production of calcitriol; responsible for the activation of vitamin D\textsubscript{3}, and cytokine response to endotoxin are the indication of its viability with proper functionality.\textsuperscript{36} Renal interstitial cells, on the other hand, produce a hormone called erythropoietin responsible for blood production.\textsuperscript{37}

A limited number of bioartificial kidney devices have been developed with viable renal cells. Examples are the renal assist device (RAD) and bioartificial renal epithelial cells system (BRECS), which use proximal tubule cells and renal epithelial cells, respectively. These devices have been involved in preclinical trials in animals in the form of extracorporeal circuit devices. They have successfully led to blood filtration and restoration of metabolic components of blood (Table 2).
Biomaterials Science

Review

Table 1  Kidney tissue growth approaches

<table>
<thead>
<tr>
<th>Cells/tissue involved</th>
<th>Source</th>
<th>Strategies</th>
<th>Results</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metanephrons; nephron</td>
<td>Murine</td>
<td>Allogenic graft of embryonic metanephrons into the anterior eye chamber and renal capsule, within the renal cortex</td>
<td>Highly vascularised</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Allograft of adult and foetal renal tissue beneath the renal capsule over the renal parenchyma</td>
<td>New formation of nephrons</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Midgestational renal graft beneath the renal capsule</td>
<td>Cytodifferentiation of glomerulus and tubular cells</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Transplantation of human foetal renal tissue</td>
<td>Graft rejection after 16 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Murine and avian</td>
<td>Creating chimeric kidney by implantaion avian and murine embryonic renal tissue to avian mesonephric mesoderm or cortex of the murine neonatal kidney</td>
<td>Adult renal tissue: rejection after 10 days</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Implantation of nephrons into tunnels fashioned in the cortex which are eventually incorporated into the collecting system when the glomeruli were vascularised, formation of proximal tubules, extension of metanephric tubules</td>
<td>Foetal renal tissue: growth and neovascularisation after 10 days, little sign of rejection</td>
<td></td>
</tr>
<tr>
<td>Tubular cells</td>
<td>Rodent</td>
<td>Encapsulating kidney cells into cross-linked gelatine microspheres injected orthotopically and conducted in vivo assessment by histological evaluation</td>
<td>Immune response of kidney rejection dependent on cell sourcing (foetal or adult)</td>
<td></td>
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<tr>
<td></td>
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<td></td>
<td>Foetal graft has allogenic response favourable for implantation</td>
<td></td>
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</tbody>
</table>

Table 2  Preclinical trials of bioartificial kidney in animals

<table>
<thead>
<tr>
<th>Animal</th>
<th>Cells involved</th>
<th>Material involved</th>
<th>Strategy</th>
<th>Results</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uremic dogs</td>
<td>Human and porcine proximal tubule cells</td>
<td>Polysulphone hollow fibres</td>
<td>Development of RAD containing human renal cells in an extracorporeal circuit</td>
<td>Increased excretion of ammonia, glutathione metabolism and 1,25-dihydroxyvitamin D3</td>
<td>17, 38</td>
</tr>
<tr>
<td>Anephric sheep</td>
<td>Renal epithelial cells</td>
<td>Porous carbon discs within carbonate housing</td>
<td>Usage of BRECS with continuous flow peritoneal dialysis circuit benefiting the peritoneal dialysis fluid to sustain the cells in the device</td>
<td>Retained neutrophil oxidative activities Improved the immunological homeostasis and endocrinal needs in uremic condition</td>
<td>36</td>
</tr>
</tbody>
</table>

Despite the favourable outcome, the cellular component of the RAD approach and BRECS only reinstates the essential metabolic activity of kidney cells. The involvement of a synthetic haemofiltration device equipped with a size-selective membrane is still essential to remove toxins from the blood. Hence, blood ultrafiltration still relies on artificial components within the system. Hence, the need to recreate a bioartificial filtration barrier to replace the synthetic unit is imperative in completing the endeavour towards developing a bioartificial kidney.

The development of a bioartificial filtration barrier mainly aims to re-establish the distinctive feature of the glomerulus in filtering blood. In addition, the presence of cells is allowing a myogenic response such as in the blood vessel, assumed to be from endothelial cells for renal autoregulation to happen in order to regulate the glomerular blood flow. The engineered construct will provide more physiological relevance to the kidney tissue engineering model.

Polymers in kidney tissue engineering

Polymers have emerged as potential materials in scaffold development in tissue engineering, including kidney tissue engineering. Their versatile properties allow easy fabrication, which is important to mimic the extracellular matrix in native tissue in terms of integrity and bioactivity. They are well-known to play an important role in creating a suitable substrate and providing structural framework to allow cell proliferation and differentiation. In kidney tissue engineering, the polymeric material should ideally possess mechanical properties that allow withstanding the shear force from blood flow and porosity to allow gaseous exchange and nutrient transport in addition to being biocompatible. Polymers can be synthetic or natural, and both type exhibit benefits towards perfecting the design of the kidney tissue engineering scaffold. Synthetic polymers are usually known for structural integrity and tailorable degradability, meanwhile natural polymers are known to be highly biocompatible for the application.
Synthetic polymers

In general, synthetic polymers exhibit tailorability and custo-
misable properties to fit a specific application. For instance,
polyactic acid and polyglycolic acid can be synthesised so that
the product would possess the specific chemical composition
needed. These can even be co-synthesised to produce polylact-
tic-co-glycolic acid in order to further broaden the range of
mechanical properties, and controlled degradation.41,42

Polysulphone. Polysulphone (PS) is a thermostable and high
mechanical strength polymer with great potential as a base
material for developing biological membranes. It is a type of
polymer with aromatic-sulphonyl monomers connected by
ether linkages and has a reputation for being biocompatible,
offering an apt blood ultrafiltration rate and is efficient in sep-
arrating target solutes (Fig. 2). Synthesis of PS is usually carried
out via a nucleophilic substitution cascade reaction between
Bisphenol A and 4,4′-dichlorodiphenyl sulphone, DCDPS.43
Neutral PS has a drawback as it can activate platelet adhesion,
leading to neutrophil production of reactive oxygen species.44

PS has significant potential in developing bioartificial
kidneys to perform haemodialysis due to its rigidity.45−47
Scientists have created a more functional material, improving
its physical attributes, such as hydrophilicity, by blending with
reactive components and surface modification.48 A clinical
study of a bioartificial kidney equipped with a PS membrane
has been created using Lewis lung cancer-porcine kidney 1 or
LLC-PK1 and Madin–Darby canine kidney (MDCK) cells
(Fig. 1). The cells were seeded onto PS coated with extracellular
matrices (ECM) such as collagen type I, laminin and pronec-
thin-F and then assessed for monolayer formation and function-
ality.49 The device managed to decrease the amount of urea,
uric acid, and creatinine by up to 50% and β2-microglobulin
under 20 mg L−1 in a human patient.50

Ongoing kidney tissue engineering studies that utilise PS
biocompatibility have led to the development of superior
bioartificial devices for haemodialysis. One study focused on
attaching two types of renal cells, human kidney 2 (HK-2) prox-
imal tubule cells and Madin–Darby canine kidney (MDCK) epi-
thelial cells, to fabricate PS hollow tubes. The tube fibres were
prepared by extruding polymer-in-solvent solution through
double injection nozzles with different diameters to create
different tube curvatures. Assessment of the water flux showed
significant ultrafiltration properties, between 190–256 L m−2
h−1, with a high bovine serum albumin rejection percentage,
\( i.e. \) above 70%. All cells managed to achieve confluent growth
on the materials. Ultimately, higher curvature or lesser dia-
meter of the hollow tubes promoted cell functionality, alleg-
edly due to mechanical stress akin to natural minuscule
tubular kidney architecture.46

Meanwhile, another PS fibre membrane fabrication was
investigated for its enhanced biocompatibility and ability to
remove uremic toxins. Before cell culture, the membrane was
coated either with a single coat of \( \nu \)-tocopheryl polyethylene
glycol 1000 succinate; or a double coating of \( \nu \)-3,4-dihydroxy-
phenylalanine (\( \nu \)-DOPA) and human collagen type IV to
improve hydrophilicity and biocompatibility towards human
blood. Human embryonic kidney cells 293 (HEK 293) were
used and observed to form a confluent monolayer on the
coated membrane, indicating improved biocompatibility. As
tested in the study, the membrane also managed to effectively
remove uremic toxins, such as urea, creatinine, and phos-
phorus, to a significantly greater extent than the commercial
PS membrane. This suggests this fibre membrane has excel-
 lent potential for developing bioartificial kidneys as a ‘living’
haemofilter.49

PS, specifically PES-50, was coated with \( \nu \)-DOPA and human
collagen type IV before cell culture involving a conditionally
immortalised proximal tubule epithelial cell (ciPTEC) line. The
optimised coating promoted water permeability and cell
monolayer formation, as well as retained proteins such as
bovine serum albumin and immunoglobulin G.51 A similar
investigation involving different fabricated PS membrane
surface designs were carried out. PS was blended with polyvi-
nyl pyrrolidinone K90 or PVP and made porous by a phase sep-
arrating micro-moulding technique,52 using a specified silicon
mould design produced by photolithography. ciPTEC were
also used in this study, cultured onto them, and observed. A
confluent monolayer was easily formed by the cells on the
membrane with small features and wider gaps without any
coating compared to the larger ones. Different topographical
arrangements of PS were concluded to have the ability to influ-
ence cell orientation and morphology, defined by the size and
gaps of micro-features that are distributed on the
membrane.53

Poly-\( \epsilon \)-caprolactone. Poly-\( \epsilon \)-caprolactone, or PCL, is a widely
known synthetic polymer in tissue engineering, especially in
bone reconstruction research and as a drug delivery material.
It is typically synthesised via ring-opening polymerisation of \( \epsilon \)-
caprolactone using a catalyst, usually stannous octanoate.54,55
Bio-based PCL is also possible to obtain through the treatment
of saccharides with ethanol or acetic acid, conversion into cyclohexanone by chromic acid and later into ε-caprolactone through a Bayer-Viliger oxidation reaction. PCL is known for its biodegradability, biocompatibility, and thermoplastic properties, with a melting point of around 60 °C. PCL is also deemed as a suitable material for developing a bioartificial kidney in kidney tissue engineering for its processability.

The work by Basu et al. assessed and compared the interaction of different kinds of polymer with kidney cells. At first, the use of PCL was not promising; direct implantation of PCL beads into healthy adult Lewis rat kidneys caused an inflammatory reaction in the first week, which continued leading to dilation and hydronephrosis after 4 weeks. Direct seeding of sunitinib-resistant renal carcinoma, or SRRC cells onto PCL also showed poor adherence after one day of culture. Despite this, modification of PCL has resulted in it becoming a suitable kidney tissue engineering material. Physical modification of PCL has been carried out by electrospinning, a method that extrudes polymer fibres with an electrical charge from melted polymer or polymer solution. Work by Burton et al. for instance, produced different types of PCL-electrospun fibres, random, aligned, and cryogenic, for kidney tissue engineering purposes. The polymer fibre scaffolds were plasma-treated to introduce hydrophilicity before cell culture. The fibres supported the growth of human kidney primary epithelial (RC-124) cells regardless of fibre orientation. However, the growth was improved with larger diameters, presumably due to a higher degree of porosity that promotes cell incorporation. Another group incorporated laminin, a component of the extracellular membrane, into the electrospun PCL to form a hybrid scaffold to enhance the bioactive properties. This scaffold supported RC124 kidney cell growth (Fig. 3). The cells were metabolically active across 21 days of culturing and showed an increase in E-cadherin expression, a component responsible for cell junction formation.

Another exciting approach is a way to use a PCL-based material with polyethylene glycol, or PEG, as a coating material. E-caprolactone was co-synthesised with PEG to produce PCL-PEG-PCL, which is more hydrophilic due to the PEG component. Neat PCL was initially prepared by Fused Deposition Modelling (FDM) to create a 3D scaffold with a criss-cross design, later spray-coated with the triblock copolymer. The coated PCL was reported to promote three times higher cell growth of embryonic kidney cells than non-coated PCL, with no cytotoxicity response.

Other PCL modification approaches to promote bio-responsive properties have been undertaken, such as surface modification with arginyl-glycyl-aspartic acid or an RGD peptide motif to enhance the cell attachment. However, this technique is yet to be explored with kidney cells as a novel functional material development.

**Polylactic acid.** Polylactic acid or PLA is another biodegradable and biocompatible synthetic polymer widely used in medical and biomedical applications (Fig. 2). It is derived...
from either lactic acid, or its cyclic dimer form called lactide, which can be synthetically produced or made from bacterial fermentation. The polymerisation of the monomer involves a water removal reaction called polycondensation, with a longer condensation period yielding higher molecular weight poly(lactic acid). In tissue engineering, PLA has its niche as a base material for scaffolds in bone tissue regeneration. Kidney tissue engineering utilising PLA has recently taken place, showing potential for PLA to be a robust biomaterial for this application.

A cytocompatibility test was carried out using primary kidney cells derived from rats on electrospun PLA fibres of different diameters. The scaffold fabrication produced fibres of different diameters; 0.88 ± 0.16 μm for small fibres, 2.46 ± 0.43 μm for medium fibres, and 3.30 ± 0.17 μm for large fibres. Furthermore, the introduction of a cryogenic condition when collecting the fibres also yielded a slightly larger fibre diameter at 3.71 ± 0.36 μm. Interestingly, this fibre was the best at supporting cell proliferation by having the highest DNA content after three and seven days of culture, which may be due to its higher porosity. Overall, protein assays confirmed the viability of four types of kidney cells on PLA, namely the proximal tubules, collecting ducts, podocytes, and glomerular endothelial cells (Fig. 4).

Another electrospinning technique was adopted to fabricate PLA for a similar application. This work addressed the hydrophobicity of PLA by adopting coaxial electrospinning with poly(vinyl alcohol) or PVA, which drastically increased the wettability by more than four times compared to neat PLA. A cell compatibility test was done using HEK 293 cells; however, it showed that neat PLA still performed as the best scaffold supporting up to 75% cell viability, compared to fabricated PLA fibres supporting only 35–40% cell viability. Even though fabricated PLA fibres do not demonstrate as high cell viability as neat PLA, SEM imaging confirmed that they do support the HEK 293 cell attachment. It is hypothesised that neat electrospun PLA produces more porous fibres that possibly influence the attachment of cells, resulting in high viability.

Polyglycolic acid. Polyglycolic acid, or PGA, is a relatively new material in kidney tissue engineering (Fig. 2). This simple polyester, like PLA, is synthesised by polycondensation of glycolic acid or by ring-opening polymerisation of cyclic dimers of glycolic acid called glycolide. Similar to PLA, the application of PGA in kidney tissue engineering is currently limited, however promising.

In a study of the effect of a 3D scaffold on glomerular cells, PGA was fabricated with fibrin gel to improve its bioactive properties upon culture. Two types of conditionally immortalized human glomerular cells were used, podocytes and glomerular endothelial cells. The unique scaffold was seeded with either mono- and co-cultures, with the co-cultures exhibiting an interesting self-assembly behaviour besides displaying good proliferation and cell adhesion patterns. Importantly, expression of collagen IV, a key glomerular basement membrane (GBM), was confirmed, showing the potential of the scaffold in developing a kidney filtration barrier.

Poly(lactic-co-glycolic) acid. Poly(lactic-co-glycolic) acid (PLGA) is a copolymer, co-synthesised from lactic acid and glycolic acid (Fig. 2), also by ring opening copolymerisation using catalysts. This novel material is well-known to be biocompatible and biodegradable. It is widely used as a drug vehicle for its tailorability erosion capability, which includes research to treat kidney fibrosis.

An assessment of PLGA as a polymer scaffold for kidney tissue engineering was done by Basu et al., who compared it with PCL. A week after injection of neat PLGA particles into the medulla and cortex of the kidney of living Lewis rats, no necrosis, embolism, or infarction was observed; however, there was chronic inflammation and formation of granulomatous cells (giant cells) around PLGA at the medulla. Meanwhile,
implantation of PLGA beads showed induced embolism and acute infraction at the cortex, as well as minimal fibrosis, chronic inflammation and also formation of granulomatous cells. However, that the implantation of a porous PLGA scaffold equipped with magnesium hydroxide as an anti-inflammatory agent and porcine renal extracellular matrix into a nephrectomised mouse kidney demonstrated the regeneration of the glomerulus, interestingly, later restoring the kidney function for the mouse.73

**Silicon.** There are limited reports on the use of silicon-based material in kidney tissue engineering. However, it has the potential as a good material to develop a bioartificial kidney. Biocompatibility tests with silicon-based materials have been successful with multiple types of cells in developing microelectronic mechanical systems (MEMS), with silicon as a semiconductor component for implantable medical devices.74,75

Several silicon-based materials have been fabricated into a nanopore membrane, adapting sophisticated step-by-step wafering and coating techniques. The fabrication involved a set of silicon-based components, namely single-crystal silicon, polycrystalline silicon, silicon dioxide, and silicon nitride. The nanopore membrane design was developed with different pore sizes ranging from 10 nm to 500 nm as a haemofilter. Initially, human cortical tubular epithelial cells (HCTC) were grown to form a monolayer, separately with each component for cytocompatibility and showed consistent and favourable growth. Meanwhile, cell behaviour on the fabricated silicon nanopore membranes allowed cell differentiation with cilia and tight junction formations.76

A strategy using a ribbed design membrane involving silicon and polysilicon components as a potential haemofilter in a bioartificial kidney has been developed.77 Surface modification of silicon has also been investigated to enhance wettability and promote cell adhesion, such as by hydroxylation.78 Although, to date, there is a lack of reported work using silicon-based kidney tissue engineering, this material exhibits the potential to be used to successfully develop a bioartificial haemofiltration membrane, which might also be a cell-seeded ‘living’ membrane on a smaller scale for transplantable devices.

**Natural polymers and biopolymers**

**Cellulose.** Cellulose is a linear polysaccharide of D-glucose units linked by β-linkages. It is a major component of the plant cell wall which provides it with rigidity (Fig. 2). There are two types of cellulose, depending on the size: microcellulose and nanocellulose.79 Both are typically extracted from plant sources; however, bacterial cellulose is a type of nanocellulose. Cellulose has been gaining attention recently as a sustainable material, used mainly as a haemodialysis membrane substitute, replacing widely used synthetic membranes and as a hydrogel for kidney tissue engineering.

There is little reported so far on utilising cellulose as a material to be used for dialysis in order to address kidney failure. MacLeod et al. compared cellulose membranes from regenerated cellulose sourced from cotton with polysulphone and showed cellulose exhibits less biocompatibility and more immune response than synthetic membranes. The authors, however, concluded that the membrane replacement did not contribute to adversity for patients undergoing haemodialysis.71,72 In other reported studies, further fabrication of cellulose into cellulose triaceta73 or cellulose diacetate74 reduced platelet activation, making it closer to the commercial dialyser membrane properties in terms of biocompatibility for a more feasible product.

In kidney tissue engineering, the involvement of cellulose-based hydrogels has been investigated as a potential scaffold for cell growth. UPM Biomedicals has developed a product called GrowDex® nanofibrillar cellulose (NFC) hydrogel for kidney organoid growth, using primary embryonic metanephric mesenchyme of murine source (Fig. 5). The material successfully provides a 3D culture of the kidney cells and demonstrates a chemically induced nephrogenesis of the organoid.75 This product is deemed a potential drug testing, disease model and a kidney development and regeneration study model.

Meanwhile, a unique approach to develop a cellulose-based scaffold for kidney tubule tissue engineering has been carried out using spinach and chive as base materials. The wet market-bought vegetables are decellularised using a 5% v/v sodium dodecyl sulfate (SDS) solution for 7 days. The scaffold is then coated with L-3,4-dihydroxyphenylalanine (L-DOPA) to introduce a bioactive surface to allow cell attachment. Conditionally immortalised proximal tubule epithelial cells (ciPTEC) were used to seed the scaffold. It is concluded that spinach and chives cellulose matrix are not favourable for fostering transepithelial solute exchange due to the micro-anatomical structure of the scaffold providing a lack of permeability.80

Further work focused on developing a functional material with cellulose, specifically using bacterial cellulose for a tissue engineering application. The cellulose was produced by fermentation of *Gluconacetobacter saccharivorans* LMG 158, in parallel fed with D-glucose and cultured with the presence of carboxymethyl cellulose sodium salt and hydroxyapatite for *in situ* incorporation. The cytocompatibility of the composite material was tested using HEK 293 cells, showing high cellular
viability up to 97.2%. However, further strategies are needed to promote cell adherence since despite the high viability of the matrix, the cells were not attaching to the BC surfaces.

**Silk.** Silk is an attractive protein-based biomaterial made of fibroin that has gained interest in tissue engineering (Fig. 6). It is typically produced by insect larvae in the form of cocoons at the stage of metamorphosis to become an adult. Generally, silk is recognised in tissue engineering for its biocompatibility, biodegradability and bioresorbable properties, in addition to its processability by spin coating, electrospinning and cross-linking. Typical silk used for tissue engineering includes silkworms from the Bombycidae and Saturniidae family, with *Bombyx mori* as a common species with high-quality fibres. Endeavours in utilising silk for research as a biomaterial in kidney tissue engineering have proven its potential to be used as a scaffold for kidney disease models.

Organoids are being increasingly used to replicate much of the complexity of an organ, and silk has proven to be a great substrate for these applications due to its high cytocompatibility as well as significant cell adhesion property. Gupta et al. successfully developed kidney organoids induced from pluripotent stem cells with a silk scaffold through spin seeding, which supported differentiation into epithelial cells from kidney progenitor cells with nephron markers (Fig. 7). Engelbart et al. successfully developed kidney organoids induced from pluripotent stem cells with a silk scaffold through spin seeding, which supported differentiation into epithelial cells from kidney progenitor cells with nephron markers (Fig. 7). Engraftment of the organoid epithelial cells under the renal capsule showed vascularisation and induced mesenchymal cell proliferation within the scaffold. Despite this model lacking the cellular organisation akin to renal tissue, further fabrication plans are possible, as demonstrated by Szymkowiak et al., who developed an aligned silk sponge by directional freezing to imitate the kidney tubule structure. This scaffold was seeded with adult proximal tubule cells and cultured in a perfused reactor, which was proven to induce cell polarity. Uregulation of key proximal tubule markers, especially SLC9A3, a sodium-hydrogen exchanger protein, was observed in the perfused condition but not in the static, indicating that the fabricated silk scaffold is necessary for maturation. Hence, this method opens the potential for a bioartificial renal assist device with a close-to-real kidney component.

For disease modelling that addresses the morphogenesis of kidney epithelial cells, silk-based scaffolds were developed to compare healthy and diseased kidneys, focusing on autosomal dominant polycystic kidney disease. Subramanian et al. used murine kidney epithelial and fibroblast cells, which were co-cultured in a collagen-Matrigel matrix to promote morphogenesis before being infused into a porous three-dimensional cylindrical silk scaffold. The cell-scaffold system was later introduced into a perfused bioreactor setup and showed better structural development than a static culture. This strategy produced a sustainable tissue model with stability for up to six weeks for both healthy and diseased cells, given the low degradation property of silk, and most importantly, allowed for tissue morphogenesis that much better mimicked what is seen in vivo. Similar work from the same research group used the 3D printing technique to generate a porous silk scaffold in which normal or polycystin-1 silenced murine inner medullary collecting duct cells were mixed with a collagen-Matrigel matrix. The use of these scaffolds showed that in the silenced Pkd1 cells, there are autocrine signalling loops which lead to unusual matrix deposition and changes in the integrin-β1 protein subunit, leading to a higher rate of cystogenesis in the tissue.

Silk has also been processed into fibres by electrospinning to serve as a tissue engineering scaffold considered biomimetic. Work performed by Mou et al. utilised podocytes...
derived from induced pluripotent stem cells and demonstrated maturation of the cells on the laminin-functionalised silk sheet for the first time with the expression of podocyte-specific markers such as podocin and nephrin. The cells were also sustained for up to two weeks.93

Hence, these results point to the utility of silk in kidney tissue engineering applications as a highly potential biomaterial.

Hydrogels in kidney tissue engineering

Bio-based hydrogels

Natural polymer-based hydrogels that have been considered suitable candidates, especially for kidney tissue engineering, include gelatin and collagen, known for manipulating the extracellular matrix protein composition.28 These materials are inherently biocompatible and non-toxic without significantly triggering immune responses within human physiology, which makes remodelling convenient. Since natural hydrogels are bio-based, they are easily functionalised to improve biocompatibility even if they are not bioactive. Also, the water retention capacity generally helps nurture cellular sustainability within a 3D structure. In kidney tissue engineering, renal researchers recognise the importance of renal cell growth, and strategies were developed to emulate an ideal cellular matrix in promoting bioactivity and cell signalling to mimic native environment.

Extracellular matrix. The extracellular matrix, or ECM, is an essential component in biological systems to allow cellular dynamics and functionality apart from maintaining structural integrity. The kidney is no exception, by comprising mainly of collagen IV, laminin, nidogen-1 and heparin sulphate proteoglycan (of perlecan, agrin and collagen type XVII),94 which maintain the specific functions of this organ. Given the kidney's complexity, different parts have different ECM compositions depending on their function and biological mechanism. The glomerular basement membrane (GBM), for instance, consists of collagen IV, laminin, nidogen, and negatively charged sulphated proteoglycan in contact with endothelial cells and podocytes, which is suited for haemofiltration.85 The GBM contains members of these protein families, including laminin-521, collagen α3α4α5(IV), and agrin and these are proven crucial for the sustaining a healthy functioning glomerulus (Fig. 8).96

Several ECM experiments have been carried out as a kidney regenerative medicine approach.94 One of the techniques is recolonising decellularised kidneys with kidney cells. The decellularisation is usually done using surfactants, normally sodium dodecyl sulphate (SDS) and Triton X-100, to wash out all cellular components leaving out only the ECM. Several types of cells have been used to recoloscise these structures, such as primary renal cells,9798 induced pluripotent stem cells,99–102 embryonic stem cells,103–105 and tubular cells106 showing positive outcomes in both supporting cell attachment and growth, as well as allowing urine production.

Kidney ECM also has been further processed and fabricated, demonstrating the processability and versatility of this biomaterial in tissue engineering applications. It has been hydrophilised and cryomilled (Fig. 9), allowing composition tailoring to make up a scaffold as a hydrogel.107–111 Blending has been adopted as well, as reported by Lih et al., who incorporated kidney-derived ECM within PLGA 3D scaffold with magnesium hydroxide to address the acidification and inflammation response.73,112 Furthermore, ECM has been successfully electrospun to mimic the filtration barrier using PCL as the base material. The ECM promoted the formation of a tight junction,113 and brush-border microvilli and cell polarisation were also observed.114 Kidney ECM has also been made into “tissue paper” that can be cut, rolled, folded and sutured, which has been proven to be very porous at 85.5 ± 1.8%, and 2.4 ± 0.8 MPa of Young’s modulus.115 Meanwhile, Matrigel, a type of ECM derived from Englebreth-Holm Swarm mice tumours consists mainly of laminin and collagen type IV, has also been used as a 3D matrix culture environment. Matrigel has the typical composition of glomerular and tubular basement membranes. In an attempt to design whole kidney tissue engineering for implantation applications, Matrigel was shown to be one of the best materials to support the branching of an isolated cellular bud derived from a rat mesonephric duct (Wolffian duct).96

Another unique approach using ECM in kidney tissue engineering is the development of bioinks. One group developed a photo-cross-linkable ECM by introducing methacrylic components along the ECM fibres. Using a heterogeneous human primary kidney cell mixture, the bioink was formulated with thermosensitive gelatin, hyaluronic acid to promote
uniform dispersion, and glycerol to assist the ink extrusion. Another bioink approach blended the ECM with sodium alginate to assist cell encapsulation which was later crosslinked by calcium chloride; in this case, using human proximal tubular cells, stem cells and human umbilical vein endothelial cells (HUVEC).

Generally, ECM, especially kidney-derived, has been shown to support kidney cell growth and proliferation with good adhesion properties. For attempts to create an ideal kidney replacement method through a tissue engineering approach, ECM is deemed as an essential component, and several approaches rely on in situ excretion by the renal cells themselves to better mimic the ECM observed in vivo.

Collagen. Another biomaterial that is gaining interest in kidney tissue engineering is collagen which forms a triple-helix protein called tropocollagen, a building block of collagen fibril that eventually becomes the collagen fibre (Fig. 10). Collagen is a major component of the kidney ECM, especially those found within basement membranes with collagen I, collagen IV (mainly in the form of α3α4α5(IV) network), collagen VI, and collagen XVIII as part of proteoglycan component. Hence, it is relevant to incorporate collagen in developing kidney tissue material formulation to obtain the best scaffold to encourage kidney cell growth and maturation. The bioactive properties of neat collagen, in particular type I collagen has been shown to restore renal function after an ischemic injury. An injected collagen hydrogel promoted glomerular and tubular regeneration, providing a simple yet effective approach to address a renal injury problem.

In terms of cell culture, collagen type I extracted from the scales of Egyptian Nile Tilapia, Oreochromis niloticas, has demonstrated cytompatibility with a baby hamster kidney (BHK-21) cell line, with no toxicity effects observed, even across different collagen concentrations (Fig. 11). In another study, collagen type I extracted from the swim bladder of grass carp has been investigated for renal tissue engineering application; initially using protein functionalised with methacrylic anhydride to allow crosslinking for structural stability and blended with chondroitin sulphate as an anti-fibrotic component. This biomimetic hydrogel has been shown to heal nephrectomised rat kidneys by promoting kidney cell growth, regenerating damaged tubular structures and restoring cellular metabolic function.

Rehydrated collagen vitrigel (collagen type I), has been prepared by vitrification, a method of drying to form a glass-like material, and has been shown to support the co-culture growth of glomerular epithelial cells with renal mesangial cells, promoting the polarisation of cells observed in vivo glomeruli. Meanwhile, the collagen-Matrigel matrix has been demonstrated as a scaffold that fostered the self-assembly of tubular and glomerular cells, with tube- and tuft-like architectures, respectively.

In a scaffold engineering approach, collagen was used to create an in vitro biomimetic branched vasculature containing kidney scaffold. Laboratory-grade collagen type I was used to coat the PCL cast perfused in a rat kidney as mould. The PCL has been washed away with acetone, leaving a hollow collagen scaffold colonised with MS-1 endothelial cells to enhance vascularisation. The 3D construct can be perfused, endothelialised and vascularised (Fig. 12).

Fig. 9 Step-by-step process obtaining ECM from kidney, (1) kidney collected, (2) cut into small pieces, (3) decellularised in SDS and Triton X-100, (4) lyophilised and ground into powder, and (5) rehydrated and solubilised. Adapted with permission from Magno et al., 2017.

Fig. 10 The building block of collagen from peptide chain to collagen fibre. Adapted from Kruger et al., 2013.

Fig. 11 Electron micrograph of collagen from Egyptian Nile Tilapia, neat collagen (left) and collagen cultured with BHK-21 (right) showing good attachment. Reused with permission from El-Rashidy et al., 2015.
Fig. 12 Branching and hollow structure of collagen vascular scaffold. The top row (A–C) shows the branching through electron microscopy, and the bottom row (D–F) shows the perfusion of trypan blue dye for the structure continuity and interconnection. Reproduced with permission from Huling et al., 2016.124

Given its bioactive property and as a naturally occurring component within almost all cellular environments, collagen is a great candidate to bring renal research forward. Whether developing a practical cell therapy approach or an ideal scaffold in tissue engineering, it provides a highly suitable tool for renal regenerative medicine.

Gelatin. Gelatin is a type of polypeptide derived from the hydrolysis of collagen fibrils. It is typically extracted from beef and pork; Isinglass is a form of gelatin from fish swim bladders with lower mechanical strength.125 Gelatin is well known for being one of the ingredients for making gel-textured desserts. It is thermosensitive with a melting point of around 30 °C, making it processable. Gelatin has been acknowledged to be biocompatible in kidney tissue engineering and has been used to develop tools to suppress certain nephropathic conditions.

For instance, a human renal progenitor cell was encapsulated in a gelatin-based hydrogel equipped with hyaluronic acid to address immunoglobulin A (IgA) nephropathy in a renal cell therapy study. The hydrogel was injected under the renal cortex of high serum IgA mice, also known as ddY or HIGA mice, a mouse strain that develops spontaneous IgA nephropathy, to enable treatment by a cell therapy approach. Injected mice were seen to have a normal appearance of the kidney with a decreased expression of pro-inflammatory and pro-fibrotic components, increased expression of anti-inflammatory genes, and much reduced IgA deposition.126 In another study, murine pluripotent embryonic stem cells were packed into a gelatin microhydrogel as a cell carrier to regenerate kidneys damaged using the 5/6 nephrectomy model of chronic kidney diseases. The cell-hydrogel was wrapped with the incised kidney by the omental flap. In the treated animals, plasma creatinine levels decreased by 30–40% and plasma urea nitrogen by 20–26% after 12 weeks, and there was a marked reduction in glomerulosclerosis and tubular injury.127 Similar work from the same group utilising mesenchymal stem cells further demonstrated that this method ameliorated fibrosis and promoted antitubular inflammation suppressing CKD progression.128

In addressing the sensitivity of renal cells towards the mechanical properties of the material, work studying podocyte behaviour was conducted using gelatin as a culture substrate. The gelatin was enzymatically crosslinked by gelatin transglutaminase to link glutamine and lysine groups, producing a biomimetic matrix akin to a healthy glomerulus, with Young’s modulus between 2–5 kPa. Interestingly, the podocytes expressed genes and proteins that reflect their specificity, differentiation, and functionality, in contrast to those cultured in a soft and stiff hydrogel.129 Gelatin was also fabricated into microspheres, crosslinked by a carbodiimide-based crosslinker solution to tune the mechanical property, in this case, to control its biodegradability. Instead of encapsulation, rat kidney cells were cultured and injected into rat kidney parenchyma. Beads with a lower degree of crosslinking were more susceptible to degradation, producing good cell performance without inducing fibrosis.35

Besides capsules and microspheres, the processibility of gelatin has enabled it to be electrospun to construct nanofibrous scaffolds. The initial hydrogel solution was formulated with an array of gelatin and acetic acid concentration ratios, in which the presence of acetic acid was to assist dissolution that leads to a tuneable electrospinning solution viscosity. A cytocompatibility test with human endothelial kidney cells, HEK 293 cells, demonstrated that electrospun gelatine scaffold with 25% acetic acid has the highest cell viability up to 90%, which was suggested to be due to the smallest amount of acid traces available, post-processing.130

In a sophisticated fabrication of a perfusable scaffold on-a-chip, a 7.5% w/v gelatin-fibrinogen matrix was housed in a microchannel formed by printing Pluronic F127 as fugitive ink. After flushing the fugitive ink, the channel was conditioned with media before being seeded with renal proximal tubular cells. They maintained the culture for over two months, with clear epithelial morphology and functionality comparable to those in 2D structure (Fig. 13).131

In terms of developing bioink, gelatin is one of the most suitable cell carriers with an ideal melting temperature that could support kidney cells.136 A bioprinting approach utilising human endothelial kidney cells, HEK293FT, has been carried out and optimised to maintain the viability of the cells by more than 90% within the hydrogel matrix. The approach has...
formulated 10% of gelatin as the main component within the bioink, along with 1% alginate and 2% fibrinogen, supporting 3D cell growth into spheroids.\textsuperscript{132}

**Alginate.** Alginate is an attractive biomaterial that is gaining attention in tissue engineering applications. As a natural polysaccharide, it is mainly extracted from brown algae despite being produced by certain bacteria from the *Pseudomonas* and *Azotobacter* genera.\textsuperscript{133} It is made up of \(\beta\)-\(\delta\)-mannuronic acid and the C5 epimer \(\alpha\)-\(\gamma\)-guluronic acid, linked by 1,4-glycosidic bonds (Fig. 14).\textsuperscript{65} Renal tissue engineering considers alginate a potential material, given its non-toxic and tailorable stiffness for soft tissue application as well as having a matrix conformation akin to ECM.\textsuperscript{134} Research involving alginate in the renal field uses it as a cell-laden matrix to mimic the extracellular environment to allow maturation.

A cell therapy experiment was carried out \textit{in vivo} and \textit{in vitro}, using a formulation of decellularised porcine kidney extracellular matrix with alginate hydrogel crosslinked by calcium chloride solution. \textit{In vitro} cytocompatibility study utilised rat renal progenitor cells, showing that a composition of 2% of alginate was optimal for supporting cell proliferation over 7 days of culture (Fig. 15). \textit{In vivo} injection of the progenitor cell encapsulated hydrogel stimulated early-stage healing by accumulating M1 and M2 macrophages, along with hydrogel degradation over 21 days.\textsuperscript{136} A similar strategy encapsulated mesenchymal stem cells into alginate microspheres coated with poly-L-lysine hydrogel construct as a graft,\textsuperscript{137} which was intended for implantation as a cell-laden scaffold into an impaired kidney. The microspheres were shown to be stationary over 25 days, with no inflammation and fibrosis, and without significant change in renal function in terms of concentration of creatinine and urea in plasma, compared to sham rats as control.\textsuperscript{138}

Alginate is also seen as a potential material to enable the engraftment of cells to a damaged kidney through advanced processing. A thiolene functionalisation technique was adapted to design an alginate-based hydrogel that is photo-crosslinkable. The soft hydrogel is an \textit{in vitro} matrix to culture kidney organoids pre-implantation. It was prepared using norbornene functionalised alginate, mixed with PEG and lithium phenyl (2,4,6-trimethyl benzoyl) phosphinate (LAP) photo-initiator, and was shown to suppress the abnormal collagen type I \(\alpha 1\) and \(\alpha\)-smooth muscle actin (\(\alpha\)SMA) production observed during fibrotic instances, nurturing proper organoid maturation \textit{in vitro}.\textsuperscript{139} Another approach designed a biomimetic matrix for organoid culture utilising oxidised alginate (alginate with the C2 and C3 bond cleaved within the hexose ring, forming two aldehyde group).\textsuperscript{140} The structurally dynamic alginate produced benefited in terms of promoting most kidney cellular segments development, tubule polarisation and cilia formation. The stress-relaxing hydrogel as well eliminated early marker of renal fibrosis.\textsuperscript{141}

Alginate was also used as a bioink in an extended application for encapsulating renal cells for 3D tissue engineering. An \textit{in vitro} kidney model was developed via bioprinting, utilising primary murine tubular epithelial cells in combination with HUVEC cells within a concentric tubular design, spatially separating the two cells in a tubular structure using a core-shell printhead. The viability of cells over seven days of culture was not promising for both commercially obtained AG-10\textsuperscript{TM} Matrix alginate and alginate from brown algae.\textsuperscript{142} It was assumed that further effort is required to make a more bio-

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**Fig. 14** Alginate general molecular structure consists of \(\beta\)-\(\delta\)-mannuronic acid (M) and the C5 epimer \(\alpha\)-\(\gamma\)-guluronic acid (G), all linked by glycosidic bonds. Adapted from Szekalska et al., 2016.\textsuperscript{135}

**Fig. 15** Cell viability test of renal progenitor cells across different ECM/alginate blend compositions, showing that 2% of alginate has the best performance over seven days of culture \textit{in vitro} where (a) CKK-8 assay and (b) confocal microscopy. Reproduced with permission from Chu et al., 2022.\textsuperscript{136}
active alginate bioink formulation. For bioengineering applications, alginate has mechanical versatility and is easily modified to improve its biocompatibility. Improving biocompatibility, especially for in vitro matrix design for renal culture, is crucial for renal tissue modelling or implantable organoid culture.

### Synthetic hydrogels

Synthetic hydrogels are defined as a type of material that is chemically synthesised, which enables it to swell and retain water, as well as form a matrix. Typically, the building block of synthetic hydrogels is synthetic polymers. Polyethylene glycol, polyethylene oxide, polyvinyl alcohol, poly(2-hydroxyethyl methacrylate) polyacrylic acid, and poly(propylene fumarate-co-ethylene glycol) are some examples of synthetic, biocompatible, and gel-forming polymers suitable for tissue engineering applications.143 To date, there are limited reports on the use of synthetic hydrogels in kidney tissue engineering. Since one of the crucial aspects to enable cell growth is for any material to be bioactive, most hydrogels selected so far for this purpose have been naturally-derived.

In the work carried out by Astashkina et al., a 3D kidney model was developed from a proximal tubule extracted from a murine kidney using a synthetic hydrogel-based matrix. Formulation of 7.5% polyethylene glycol dimethacrylate (PEGDA) and 1.5% thiol-modified carboxymethylated hyaluronic acid (CMHA-S) to introduce a bioactive environment, made up of the hydrogel to enable a 3D culture of the cells. The organoid formed is claimed to maintain cellular activity observed in vivo and was stable for up to six weeks, which is relevant for a drug screening model focusing on nephrotoxic effects.144,145 Clerkin et al. developed an organic-based synthetic hydrogel, gelatin methacryloyl, widely known as GeMA, to grow iPSC-derived kidney organoids. It has been shown to nurture the development of both distal and proximal tubular structures as well as the glomerulus, with gene expression analysis showing upregulation of nephron-related genes, including PAX8, NPHS2, NPHS1, SLC3A1 and AQP1.146

Synthetic hydrogels are the future of tissue engineering, with the possibilities of tailoring an ideal cell culture matrix. However, their bioactive properties still need to be properly addressed. Generally, cells in microenvironment need biochemical cues and signals that promote proliferation and differentiation in order to be fully functional. Kidney cells for instance respond well with presence of bioactive materials such as collagen118–120 and laminin, both of which are integral in healthy kidney tissues. Other types of biomolecules that can be considered include RGDb-peptides to improve cells attachment onto the substrate,62 and growth factors such as vascular endothelial growth factor, or VEGF, especially for glomerular endothelial cells in order to promote vascularisation.147 Kidney extracellular matrix is one of the biomaterials that proven to nurture kidney cells, given all of its composition allow kidney cells to stay viable to become fully functional.

Hence, synthetic hydrogels are yet to be explored for their potential in kidney tissue engineering. The strategy for the enhancement of their biocompatibility and bioactivity by the incorporation of certain compounds in order to enable cell–matrix interaction and ultimately promote a better design for kidney regenerative application (Table 3).

### Conclusion and future prospective in kidney tissue engineering

Kidney tissue engineering is rapidly growing with the aim of producing the closest imitation to an organ that performs hae-mofiltration and complements biochemical processes to restore the innate physiological balance. Any tissue engineering attempt acknowledges the importance of creating a suitable base for regenerating functional tissue, whether it provides mechanical integrity to support appropriate cell proliferation and differentiation or creates a viable microenvironment; both are equally important.

#### Suitability of polymers and hydrogels

Polymers and hydrogels are common materials used for kidney tissue engineering, widely tailored to optimise using the combination of multiple materials to achieve the best composition and formulation. Polymers, for instance, need to be appropriate for soft tissue engineering applications, which is important for a kidney. A material that is too stiff may affect proper cell development, as observed in the culture of podocytes.129 A bioactive substrate that supports growth and differentiation, is a major aspect of the material composition. In most cases, ECM derived from the kidney or Matrigel91,92,96 have been extensively utilised. Using other bioactive components such as hyaluronic acid116,126,144 and fibrin40,131,132 has also created a better renal cell growth environment. Hence, work carried out shows that renal tissue engineering is feasible in generating a cellurally functional kidney tissue that can perform the intended function within the human body. Silk has a special ability to support kidney cell growth without any further modification as described in this review.89–92

Each material category offers specific benefits and addresses different aspects in kidney tissue engineering. Hence, to state that one type of material is superior to another would be inaccurate. They complement each other and hence, multi-material structures are a way forward to creating the best material formulation.

#### Challenges in developing bioartificial kidney

A step forward will be the use of these materials in a medical setting, either developing a practical and effective regenerative therapeutic approach to repair partially degenerated kidneys or a functional bioartificial kidney to replace damaged kidneys. For bioartificial kidneys, the renal cell biology needs complement the physical aspect of a natural kidney with fluid flow and dynamics, to adequately address the functionality and stability of the cells. The design needs to address the intricacy.
Table 3: A summary of table of materials that have been used in kidney tissue engineering

<table>
<thead>
<tr>
<th>Material</th>
<th>Modification</th>
<th>Cell Line</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polysulphone (PS) Coated with extracellular matrices (ECM) such as collagen type I, laminin and pronectin-F</td>
<td></td>
<td></td>
<td>Significant ultrafiltration properties were achieved, between 190 – 260 kDa, with a high degree of porosity.</td>
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<tr>
<td>Human embryonic kidney cells 293 (HEK 293) E</td>
<td></td>
<td></td>
<td>Created hollow tubes by extruding polymer-in-solvent solution through double-injection nozzles with different flow rates.</td>
</tr>
<tr>
<td>Human kidney primary epithelial (RC-124) cells</td>
<td></td>
<td></td>
<td>Electrospun fibers: random, aligned, cryogenic and plasma treated.</td>
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<tr>
<td>Poly(ε-caprolactone) (PCL) Coaxial electrospinning with polyvinyl alcohol (PVA)</td>
<td></td>
<td></td>
<td>Electrospun fibres: random, aligned, cryogenic and plasma treated.</td>
</tr>
<tr>
<td>Polylactic acid (PLA) Electrospinning with different fibre diameters</td>
<td></td>
<td></td>
<td>Pore sizes ranging from 10 nm to 500 nm as a result of the varying process parameters.</td>
</tr>
<tr>
<td>Electrospinning: random, aligned, cryogenic and plasma treated</td>
<td></td>
<td></td>
<td>Electrospinning: random, aligned, cryogenic and plasma treated.</td>
</tr>
<tr>
<td>Blended with polyvinyl pyrrolidinone K90 (PVP) and made porous by a phase separating micro-moulding technique</td>
<td></td>
<td></td>
<td>Electrospinning: random, aligned, cryogenic and plasma treated.</td>
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<tr>
<td>Coaxial electrospinning with polyvinyl alcohol (PVA)</td>
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<td></td>
<td>Electrospinning: random, aligned, cryogenic and plasma treated.</td>
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<tr>
<td>Porous PLGA scaffold containing magnesium hydroxide as an anti-inflammatory agent</td>
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<td>Fabrication of cellulose into cellulose triacetate and cellulose diacetate.</td>
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<tr>
<td>Fabrication of cellulose into cellulose triacetate and cellulose diacetate</td>
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<td>Electrospinning with different fibre diameters.</td>
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<tr>
<td>Nanofibrillar cellulose (NFC) hydrogel</td>
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<td>Electrospinning with different fibre diameters.</td>
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<tr>
<td>Polyurethane and polyethylene glycol (PEG) Hydrolysis</td>
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<td>Electrospinning with different fibre diameters.</td>
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<tr>
<td>Natural polymers and biopolymers</td>
<td></td>
<td></td>
<td>Electrospinning with different fibre diameters.</td>
</tr>
<tr>
<td>Cellulose Cellulose membranes from regenerated cellulose sourced from cotton blended with polysulphone</td>
<td></td>
<td></td>
<td>Electrospinning with different fibre diameters.</td>
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<tr>
<td>Decellularised spinach and chive leaves coated with natural polymers and biopolymers</td>
<td></td>
<td></td>
<td>Electrospinning with different fibre diameters.</td>
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<tr>
<td>Aligned silk sponge by directional freezing; introduced in a perfusion bioreactor</td>
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<td></td>
<td>Electrospinning with different fibre diameters.</td>
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<td>3D printing technique generated a porous silk scaffold</td>
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<td>Kidney organoids from induced pluripotent stem cells (iPSC)</td>
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<td>Adipose progenitor cells</td>
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<table>
<thead>
<tr>
<th>Material</th>
<th>Bio-ink formulation</th>
<th>Cell line</th>
<th>Results</th>
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<td>Collagen-Matrigel matrix</td>
<td>Mixed neonatal rat renal cells</td>
<td>Fostered the self-assembly of cells, with tube-like structure containing CK18-positive renal epithelial structures</td>
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<td>Gelatin</td>
<td>Gelatin-based hydrogel with hyaluronic acid</td>
<td>Human renal progenitor cell; injected under the renal cortex of mice with high serum IgA (ddY or HIGA mice)</td>
<td>Plasma creatinine levels decreased by 30–40% and plasma urea nitrogen decreased by 20–30%. There was a marked reduction in glomerulosclerosis and tubular injury progression. Podocytes Expressed genes and proteins that reflect their specificity, differentiation, and function.</td>
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<td>Alginate microspheres coated with poly-β-hydroxybutyrate</td>
<td>Renal proximal tubular cell</td>
<td>Maintained the culture for over two months</td>
<td>Clear epithelial morphology and functionality comparable to those in 2D structure. No inflammation and fibrosis.</td>
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<td>Photo-cross-linkable porcine kidney ECM bioink by introducing methacrylic anhydride</td>
<td>Immortalized porcine LLC-PK1 renal proximal tubule epithelial cells HEK 293 and RPTEC</td>
<td>High cell viability and metabolic activity in an appropriate arrangement led to the formation of cell monolayers without any sign of cell death. No inflammation and fibrosis observed during fibrosis.</td>
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of the natural kidney architecture, to allow proper functionality. Further, the challenge continues with the need to sustain the cells by integration within the patient's physiological system. This is also accompanied by immunological issues. Also, the bioartificial kidney unit should last for a significant amount of time to avoid frequent interventions which would still affect the patient's quality of life. Finally, regulatory issues for the unit's viability, reliability, and safety need to be addressed to allow patients to have a clinically approved approach. This endeavour is thus challenging but not unrealistic, given that some prototypes have already been used in animal trials, suggesting that they only need to be further refined for a human clinical trial.

Author contributions


Conflicts of interest

There are no conflicts to declare.

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