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SARS-CoV-2 and tissue damage: current insights and biomaterial-based therapeutic strategies

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The effect of SARS-CoV-2 infection on humanity has gained worldwide attention and importance due to the rapid transmission, lack of treatment options and high mortality rate of the virus. While scientists across the world are searching for vaccines/drugs that can control the spread of the virus and/or reduce the risks associated with infection, patients infected with SARS-CoV-2 have been reported to have tissue/organ damage. With most tissues/organs having limited regenerative potential, interventions that prevent further damage or facilitate healing would be helpful. In the past few decades, biomaterials have gained prominence in the field of tissue engineering, in view of their major role in the regenerative process. Here we describe the effect of SARS-CoV-2 on multiple tissues/organs, and provide evidence for the positive role of biomaterials in aiding tissue repair. These findings are further extrapolated to explore their prospects as a therapeutic platform to address the tissue/organ damage that is frequently observed during this viral outbreak. This study suggests that the biomaterial-based approach could be an effective strategy for regenerating tissues/organs damaged by SARS-CoV-2.

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1 Introduction

SARS-CoV-2, a potent and highly contagious virus, is posing a major health threat and affecting the global economy.[1–3] An outbreak of "pneumonia of unknown origin" in Wuhan was confirmed to be associated with coronavirus,[4] and the disease was named coronavirus-induced disease 2019 (COVID-19) by the WHO. Coronavirus primarily targets the respiratory system.[5] Previous outbreaks of coronaviruses include severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). Globally, by 26th November 2020 a total of 61 308 613 confirmed cases of COVID-19, including 1 437 840 deaths, had been reported by the WHO.[6]

Coronaviruses are the largest known RNA viruses, with a diameter in the range of 65–125 nm and a nucleic acid genome that is 26–32 kb in length.[7] Like other similar viruses, COVID-19 has multiple hosts, including natural, immediate and final hosts, which pose a major challenge to its prevention and effective treatment. Compared with SARS and MERS,

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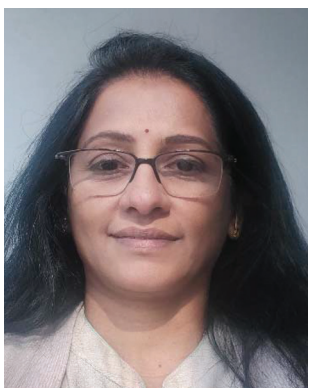
COVID-19 has high infectivity and transmissibility and low mortality.[8] Most COVID-19 patients are asymptomatic or display mild symptoms, such as sore throat, mild fever and dry cough. While majority of the infected patients recover, some patients develop complications such as pulmonary oedema, septic shock, pneumonia, acute respiratory distress and multiple organ failure, which can be fatal.[9] Notably, older patients with multiple comorbidities, including cerebrovascular, cardiovascular, digestive, endocrine and respiratory disease, need intensive care support.[10]

To date, the efficacy of the few vaccines that have been approved against COVID-19 as preventive measures is yet to be determined against mutating strians. An understanding of the mechanism of infection and of the impact of the virus mutations on host immunity is essential, both to facilitate the development of efficient vaccines as well as its detection techniques.[11–13] In addition, there is an urgent need to develop therapeutic options for preventing and/or replacing damaged cells and tissues in patients severely affected by the virus. Biomaterials provide a wide-ranging therapeutic opportunity to induce the repair of damaged tissues in such conditions. The use of these biomaterials at the damaged site can attract the surrounding cells and provide the necessary conditions for normal growth of the cells, leading to tissue regeneration and preventing further organ damage. The present study aims to briefly consider biomaterials as a therapeutic opportunity for tissue regeneration to prevent further cell damage caused by SARS-COV-2.

2 Genetic structure of SARS-COV-2

Coronaviruses are classified into four types: α coronavirus, β coronavirus, γ coronavirus and δ coronavirus.[14] SARS-COV-2, like MERS and SARS COV, is a β coronavirus. There is 96% genomic similarity between SARS-COV-2 and SARS coronavirus derived from bats, which suggests that SARS-COV-2 may have originated from bats. SARS-COV-2, like SARS COV, uses angiotensin-converting enzyme 2 (ACE2) as its receptor,[15] but its affinity is 10-fold higher than that of SARS-COV.[16] The viruses recognize the host receptors with the help of the S proteins located on their surface to gain entry into host cells. Considering the fact that SARS-COV-2 has a very high affinity for ACE2, ACE2 may be a considered as a promising target for the treatment of COVID-19.



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3 Clinical characteristics of SARS-COV-2 infection

In humans, an acute infection is observed within a median incubation period of 3–4 days.[17] The most common characteristics of COVID-19 are cough, fever and fatigue. Although many patients have dyspnoea, the symptoms are more pronounced in adults.[18] In severe cases, patients display complications such as acute heart injury, respiratory distress syndrome and secondary infections.[9] Most of the severely affected cases have comorbidities such as acute heart injury, arrhythmia, abnormal liver function, impaired renal function, neurological manifestations *etc*. at the time of admission.[19,20]

4 Pathophysiology

The pathophysiology of COVID-19 is not yet fully understood. As ACE2 receptors are ubiquitous in the alveolar epithelial type 2 cells of lung tissue and other extrapulmonary tissues such as the heart and kidneys, they are considered to play a central role in multi-organ susceptibility to COVID-19 infection.[21] SARS-CoV-2 affects the lower respiratory tract and causes severe pneumonia.[18] Following its binding to ACE2, the cellular transmembrane protease 2 mediates the S protein, allowing the virus to enter the host cell *via* endocytosis. Following its entry into the host cells, the virus exploits the cellular machinery to replicate itself and spread throughout the host.[22,23] The S protein mediates the fusion of viral and host membranes and contains a receptor-binding domain (RBD) that attaches to cells during virus entry.[24] The virus alters the behaviour of the host cell by utilizing the endogenous transcriptional machinery and disrupting the cell's normal functioning (Fig. 1). When infection with SARS-CoV-2 occurs, it initiates the primary innate and adaptive host immune responses in the body. A failure of the host immune response results in inflammation.[25] The innate immune response is observed in the initial stage, and is followed by the adaptive immune response, which occurs during the early stages of incubation to prevent the progression of the infection. However, when the immune response becomes ineffective, the virus propagates and causes massive destruction of the affected tissues, leading to further uncontrolled inflammation. Significant increases in blood levels of chemokines and pro-inflammatory cytokines have been reported in COVID-19-infected patients.[9] It has been

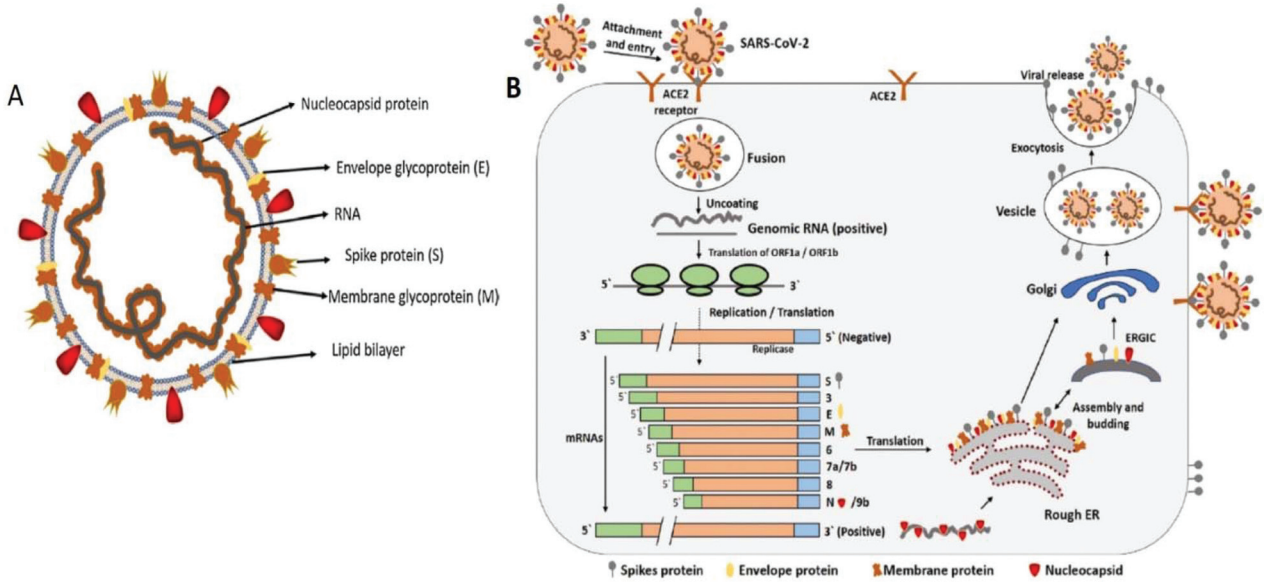

Fig. 1 (A) Structure of the human coronavirus causing respiratory syndrome. (B) Life cycle of SARS-CoV-2 in host cells. Reproduced from ref. 7 with permission from [Elsevier], copyright [2020].

hypothesized that the virus spreads through the respiratory mucosa and infects other cells, resulting in a cytokine storm that induces necrosis or apoptosis of T cells and generation of multiple immune responses.[9] In several acute cases, patients with acute respiratory distress syndrome and septic shock have succumbed to multiple organ failure.[26]

5 Therapeutic opportunities to use biomaterials for tissue repair in COVID-19

As a result of the ongoing second wave of COVID-19 infection, addressing tissue damage caused by SARS-CoV-2 has become an important area of biomedical research. As summarized in Fig. 2, COVID-19 leads to tissue damage and multiple organ failure, which ultimately results in the patient's death. In view of the observed tissue damage in COVID-19 patients, a promising approach to supporting tissue repair is by employing biomaterials as scaffolding materials. Biomaterials have been used as a component in the engineering of a range of tissues, such as tendons, ligaments, bladder, kidneys, liver, heart, bone, cartilage, pancreas, vascular tissue, skin *etc*[27] The following sections provide an overview of the various biomaterials that have been used for tissue regeneration.

5.1 Biomaterials for pulmonary tissue engineering

There is increasing evidence that the lung is the most vulnerable target organ of SARS-CoV-2, with type II alveolar epithelial cells expressing 83% of the total ACE2 receptors. During the initial stages of COVID-19 infection, the symptoms are non-specific, which is typical of multiple respiratory illnesses. While most cases are mild, with recovery occurring within 2 weeks, patients with severe infection display symptoms that closely resemble those of SARS and/or MERS infections.[28] Patients with severe pulmonary problems, such as lung cancers, cystic fibrosis and pulmonary hypertension, are considered to be at high risk in view of their compromised status. The treatment options that are currently available are limited to mechanical support systems such as ventilators and extracorporeal membrane oxygenators (ECMO).[29,30] Although these provide effective support for the majority of such patients, in some cases they merely provide a temporary means of sustaining the patient until lung transplantation is possible. With limited availability of organ donors, progress in the area of tissue engineering and regenerative medicine appears to offer a promising alternative.[31] Biomaterials can play an essential role in providing the same niche and microenvironment for tissue regeneration.[32] Biomaterials that are used for lung tissue regeneration should be biocompatible, porous and biodegradable, and have mechanical properties that match those of native, healthy lung tissue.[33]

5.1.1 Polymers. Polymers are extensively used as a biomaterial for supporting tissue repair and regeneration.[34,35] Polymers that are used in lung tissue regeneration include the following: (a) natural polymers, such as collagen, fibrin, hyaluronic acid, alginate, chitosan, gelatin, silk, fibronectin, growth factors *etc.*; (b) synthetic polymers, such as poly(glycolic acid), poly(ε-caprolactone), poly(lactic-*co*-glycolic acid), poly (ethylene glycol), poly(vinyl alcohol), poly(acrylic acid) poly (lactic acid) *etc.*; and (c) their hybrids, such as elastin fibres in combination with a mixture of polyglycolic acid/polylactic

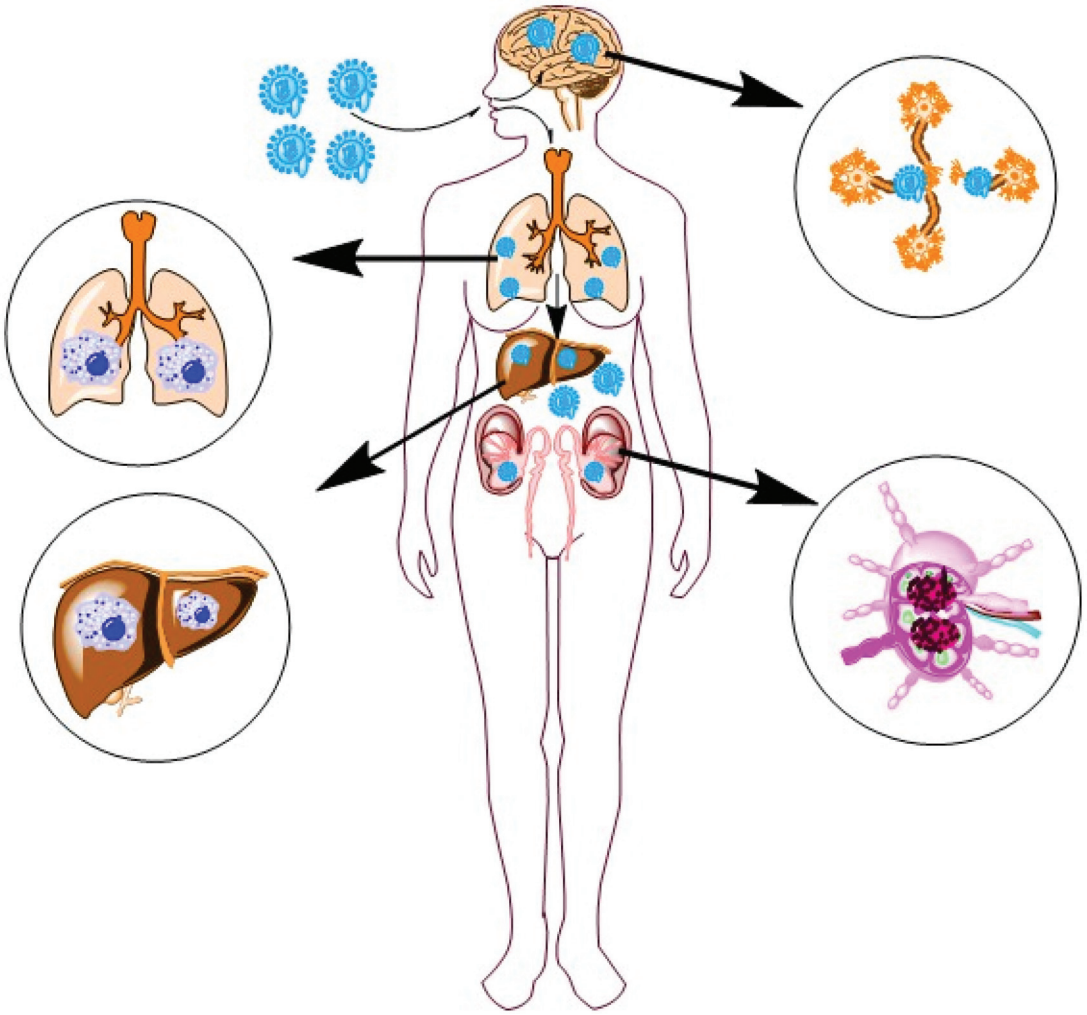

Fig. 2 Effect of SARS-CoV-2 on organs.

acid,[36] and commercial benzyl ester in combination with hyaluronic acid.[37] Hydrogels composed of polyvinyl alcohol (PVA), poly(ethylene glycol) and elastomers[38] such as poly(glycerol sebacate) (PGS)[39] have been used to mimic the native lung architecture. Despite studies that have reported the use of albumin from various sources (including porcine, human and bovine),[40,41] collagen-based hydrogels are the most popular biomaterial reported for *in vitro* respiratory tissue engineering. In one of these studies the use of collagen hydrogel reportedly led to the formation of alveolus-like structures.[42] A collagen concentration of 2–3 mg ml^{-1} was able to prevent excessive fibroblast-induced contraction in a co-culture model.[43] Collagen in combination with glycosaminoglycan was used for the construction of alveolus-like structures.[44] The immunocompatibility of a chitosan–gelatin hydrogel was demonstrated using macrophages, and the material supported the growth of human respiratory epithelial cells.[45] The addition of elastin to a collagen hydrogel increased the stiffness and mechanical properties of the hydrogel, leading to improved differentiation and proliferation.[33,46] Recent studies have revealed a significant link between COVID-19 and chronic obstructive pulmonary disease (COPD).[47,48] It has been shown that deregulated angiogenesis is a major pathological condition in COPD.[49] Therefore improving lung-specific angiogenesis would be beneficial for the development of more efficient methods for lung tissue engineering.[50] To improve angiogenesis, fibrin fibrils with the ability to trap angiogenic factors such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) have been utilized (Fig. 3).[50] It has been shown that prolonged COPD can be associated with tracheobronchomalacia (TBM).[51] To address this disorder, Hollister *et al.* implanted a biodegradable 3D-printed bio-resorbable airway splint that underwent natural cartilage remodelling.[52] This splint was later successfully tested in the treatment of TBM (Fig. 4).[53,54]

Scaffolds prepared with synthetic materials have been tested for tracheobronchial tissue regeneration. PGA and pluronic F-127 hydrogels seeded with adult lung progenitor cells (SLPC) are reported to express lung-specific markers.[55] In another approach, epithelial cells, fibroblasts and dendritic

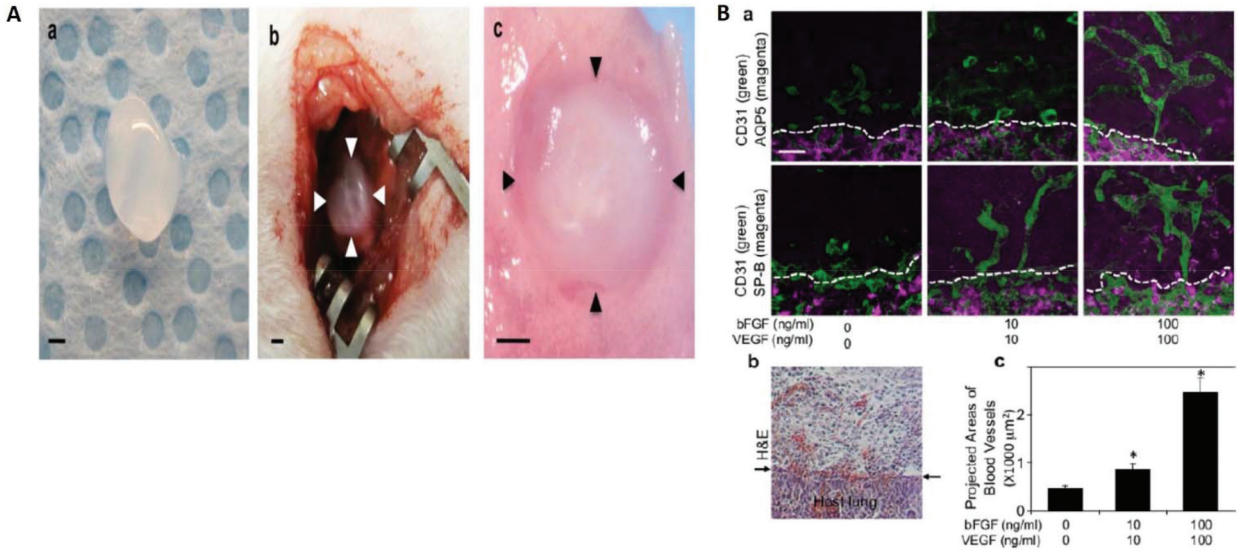

Fig. 3 (A) (a) Fibrin gel prepared before implantation. (b) Fibrin gel implanted over the scraped visceral pleura of the left lung (arrowheads). (c) Implanted fibrin gel (arrowheads) incorporated into the host lung 7 days after implantation. Scale bars: 1 mm. (B) (a) Fluorescence micrographs showing formation of vascular networks (CD31 positive; green) and recruited type I (AQP5-positive; magenta) or type II (SP-B positive; magenta) lung epithelial cells inside the fibrin gel supplemented with different concentrations of VEGF and bFGF (0, 10 and 100 ng ml^{-1}) 7 days after implantation. Dashed lines indicate the interface between implanted fibrin gel and host lung. Scale bar: 20 μm. (b) Light micrograph of H&E staining showing infiltration of host cells into the fibrin gel 7 days after implantation. Arrows indicate the interface between the gel and host lung. Scale bar: 20 μm. (c) Graph showing projected areas of newly formed blood vessels in the fibrin gels that are supplemented with different concentrations of VEGF and bFGF (0, 10 and 100 ng ml^{-1}) 7 days after implantation. Reproduced from ref. 50 with permission from [Jove], copyright [2014].

cells were seeded on electrospun polyethylene terephthalate (PET) mats before being assembled to create an immunocompetent triculture system with appropriate cell localisation.[56] Besides individual natural and synthetic biopolymers, there are many hybrid polymers that are used in lung TE. Radhakumary *et al.* reported an interesting hybrid scaffold composed of hyaluronic acid and poly(HEMA). The latter, used in biological processes, is permeable to metabolites, has a high water content and is non-degradable. The hybrid matrix supported the growth of multiple cell types, including alveolar cells.[57] A cryogel prepared using a combination of alginate, gelatin and hydroxyethyl methacrylate (HEMA) was used for lung tissue regeneration.[58] Due to the biodegradability of the alginate and gelatin components of the cryogel, the need for surgical intervention to remove the implanted hydrogel was avoided.[59,60] The cryogel could recruit cells from the surrounding tissues, leading to successful growth of lung cells. In another approach, a biocompatible hybrid scaffold comprising poly(ε-caprolactone) (PCL) and gelatin exhibited increased mechanical strength with increased cellular proliferation and cellular metabolic activities.[61] An implant consisting of L-lactide and ε-caprolactone supported cell migration and degraded within 2–3 months following its *in vivo* implantation.[62,63]

As well as such modifications, the use of nanotechnology in polymer science has provided greater opportunities for advances in biomedical science. The most common nanostructures used in TE are fullerenes, dendrimers, hydrogels, aerogels, nanorods, nanocomposites, nanowires, nanofibers, nanoparticles, quantum dots *etc*.[35,64–68] Nanofibers exhibit better physical and mechanical properties. They have improved cell adhesion properties due to their high porosity which simulates the extracellular matrix (ECM) and makes them suitable for tissue regeneration, drug delivery, wound dressing and medical prostheses. Biocompatible nanofibers made with PCL/chitosan retain their structural and mechanical integrity.[69] The tensile strength of PCL/chitosan is reported to be much higher than that of PCL-based composite scaffolds for tracheal bioengineering.[70]

5.1.2 Bioceramics. Bioceramics prepared from calcium phosphates, glass–ceramics, *etc*. are used for the reconstruction and repair of tissues. Previously, these biomaterials were used to repair hard tissues, such as dental and bone defects. Recently, however, they have been used to repair soft tissues such as skin, pulmonary tissue and nerve tissue.[71] Bioceramics are reported to support cell proliferation and differentiation, enhance angiogenesis, and exhibit antibacterial/anti-inflammatory activity. In addition, these materials improve the mechanical properties of the implant when embedded in a soft matrix. The efficacy of bioceramics in the healing of skin wounds has been confirmed in pre-clinical trials.[72]

Bioactive glass (BG) used in soft TE showed promising results with regard to supporting cell growth of vital organs such as the heart and lungs.[73–76] BG is composed of borosilicate, silicate-based glasses, phosphate-based glasses and borate-based glasses. Doping of BG with metallic ions elicits specific therapeutic effects. In the first study on the use of BG for lung tissue repair, scaffolds made with 58S (58 SiO2–36

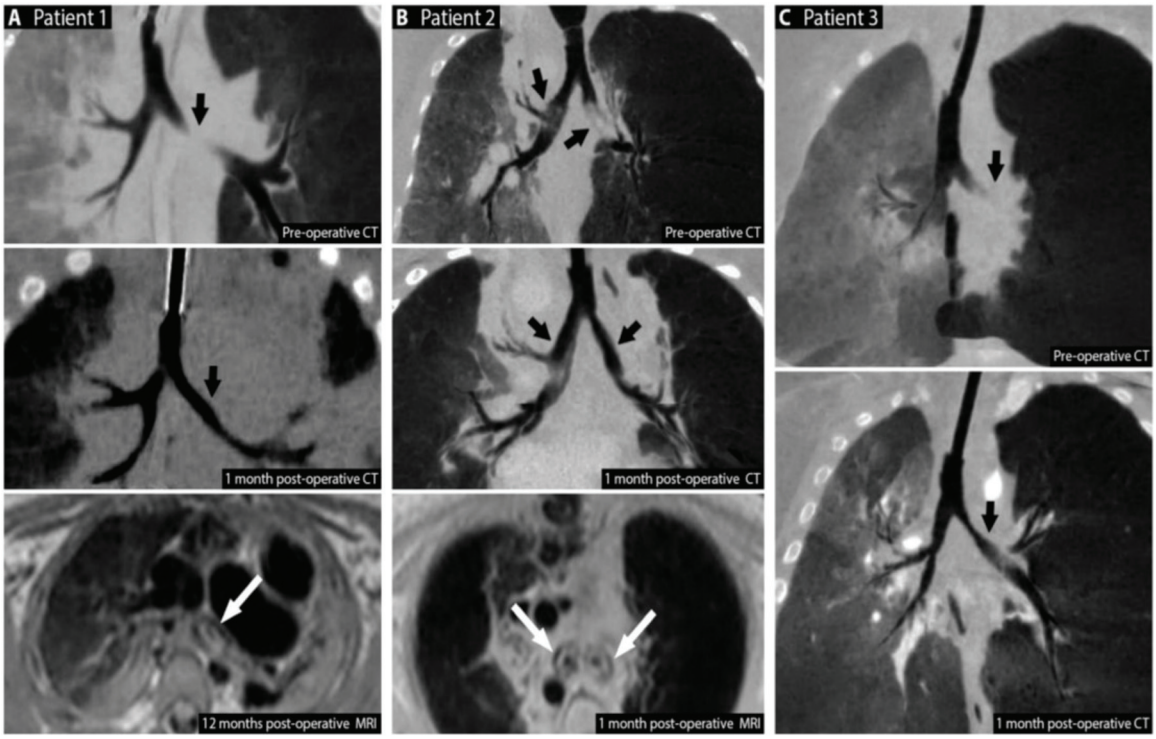

Fig. 4 Pre- and postoperative imaging of patients. Black arrows in all figures denote the location of the malcic segment of the airway. White arrows indicate the location/presence of the tracheobronchial splint. Asterisk denotes focal degradation of the splint. All CT images are coronal minimum intensity projection (MinIP) reformatted images of the lung and airway on expiration. All MRI images are axial proton density turbospin echo MRI images of the chest. (A) Preoperative (top) and 1-month postoperative (upper middle) CT images of patient 1. Postoperative MRI (lower middle) demonstrated the presence of the splint around the left bronchus in patient 1 at 12 months, and focal fragmentation of the splint due to degradation at 38 months (bottom). (B) Preoperative (top) and 1-month postoperative (upper middle) CT images of patient 2. Postoperative MRI (lower middle) demonstrated the presence of splints around the left and right bronchi in patient 2 at 1 month. Note that the patient had bilateral mainstem bronchomalacia and received a tracheobronchial splint on both the left and right mainstem bronchi. (C) Preoperative (top) and 1-month postoperative (bottom) CT images of patient 3. Reproduced from ref. 53 with permission from [Science], copyright [2015].

CaO-6 P2O5) were reported to support the proliferation and growth of murine lung epithelial cells (MLE-12).[77] Subsequently, a porous BG composite made of poly(DL-lactic acid) (PDLLA)/45S5 Bioglass® was shown to support lung cell proliferation, which confirmed its cytocompatibility.[78] A porous composite made with PDLLA/45S5 Bioglass® supported proliferation of the lung carcinoma A549 cell line, with a dose-dependent increase in cell adhesion observed within 2 h with increasing content of Bioglass® (0, 5, and 40 wt%).[78]

5.1.3 Extracellular matrix. SARS-CoV-2 causes severe illness in 20% of patients. This could also be due to the uncontrolled immune response to SARS-CoV-2 infection triggering a systemic hyper-inflammatory response – the so-called "cytokine storm". The reduction of this inflammatory immune response could be considered as a potential therapeutic target against severe COVID-19. To control the cytokine storm, many immunomodulators or immunosuppressors have been investigated.[79] In this context, ECM-based biomaterials are a possible option for inducing immunosuppression with simultaneous tissue repair. It has been shown that scaffolds prepared with ECM can modulate the behavior of immune cells toward an anti-inflammatory phenotype.[80] Scaffolds made with xenogeneic-ECM are reported to promote a Th2-restricted response through the release of anti-inflammatory cytokines such as interleukin (IL)-4, IL-10 following their implantation in a murine host.[81] Implantation of ECM scaffolds has been reported to elicit a favorable host innate immune response, which is required for tissue regeneration.[82] The immunomodulatory effects of ECM are exerted not only by directly influencing macrophage phenotype, but also through paracrine factors that mediate macrophage cross-talk with endogenous stem/progenitor cells.[83,84] Coating of ECM proteins on polypropylene mesh has mitigated the chronic inflammatory response and associated downstream scar tissue formation after implantation. Similarly, the addition of an ECM hydrogel coating on polypropylene fibers resulted in a decrease in the number of pro-inflammatory CD86+/CD68+ macrophages in the vicinity of the material 2 weeks after implantation. Six months later, a remarkable decrease in collagen deposition was observed, indicating reduced fibrosis.[85] Hybrid hydrogels have also been evaluated for their ability to modulate the immune response. A poly(ethylene glycol) (PEG) hydrogel containing a peptide mimic of the TNF-α recognition loop was evaluated as a cell encapsulation material. Since the hydrogel

could sequester TNF-α, the encapsulated cells were protected from the pro-inflammatory cytokines.[86] Based on these studies, ECM can be used as an immunomodulator in COVID-19 patients.

Besides its role as an immunosuppressor, ECM can be used in cell growth and TE. The lung's unique ECM provides the cells with structural support, which is critical for the regulation of developmental homeostasis, organogenesis and tissue-repair responses.[87] The ECM, *via* biomechanical and biochemical cues, regulates the cell's fate as well as its phenotype and diverse cellular functions. The function and composition of ECM in the lungs are disrupted under pathological conditions.[88] For ECM to be used as a scaffolding material, it should be as porous and elastic as normal lung tissue in order to provide the optimum environment for cell growth.[89] Natural materials that have been used to grow lung tissue include collagen,[42,44] Matrigel[90,91] and Gelfoam.[31,92] *In vivo* studies using these scaffolds have demonstrated their potential to support tissue growth, although the development of lung tissue using these materials has not been substantial.[31,91] It is well known that the elasticity of the matrix influences stem cell differentiation. Matrix elasticity influences the differentiation potential of MSCs to a particular cell lineage.[93] Similarly, the influence of ECM on cell differentiation was confirmed by the differentiation of mouse embryonic stem into airway epithelial cells.[94] Thus ECM-based therapy and bioengineering approaches could be a promising strategy for the rapid regeneration/repair of lungs that have been damaged by SARS-CoV-2. In a study using stereolithography, a hydrogel made of tartrazine or curcumin was used to print a vascularized alveolar model. Studies indicated that it could function like a human lung, by demonstrating its ability to mix oxygen with red blood cells (RBCs) when the air sac was ventilated with oxygen.[95,96]

Recently, 3D self-organized tissue structures (organoids) that mimic the structural, chemical and physiological characteristics of organs have been developed *in vitro* as a promising approach for tissue regeneration.[97] These organoids are obtained from various cell types, such as embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs) and adult stem cells. To develop the organoids, the cells are seeded on biomaterials.[98] The most commonly used biomaterial for formation of lung organoids is Matrigel.[99,100] Using the latter, human alveolar epithelial progenitors (AEPs) together with lung fibroblasts have been co-cultured to form functional alveolar epithelial cells.[101] Similarly, lung organoids have been developed in Matrigel following the culture of lung fibroblasts together with human somatic primary bronchial epithelial cells and lung microvascular endothelial cells.[102]

5.2 Biomaterials for urological tissue engineering

Besides its effect on the pulmonary tract, SARS-CoV-2 reaches other organs where it causes cell and tissue damage that results in impaired functioning of those organs, leading to organ failure. Initial reports from Wuhan, China showed that approximately 3–9% of hospitalized COVID-19 patients showed acute kidney injury (AKI). The rate of AKI in COVID-19 patients that require dialysis treatments has now increased from 15% to 30%.[103] AKI has been found to be a symptom of COVID-19 infection with a higher severity and mortality rate. On infecting the renal tissue, COVID-19 causes AKI, which includes kidney tubular injury (acute tubular necrosis) with septic shock, increased blood clotting and micro-inflammation.[103] Other effects include mild proteinuria, haematuria and elevated creatinine levels as a consequence of kidney tropism of the virus and multi-organ failure. Patients who have recovered from COVID-19 have shown impaired kidney function as a result of AKI and chronic kidney disease (CKD).[103,104] Biomaterials have been tested for their potential application in tissue repair in many renal failure scenarios, and can be used to induce tissue repair in COVID-19 patients.

5.2.1 Acellular matrix. Classical methods employed to induce kidney regeneration include coating of polymers with growth factors.[105] To encourage tubular cell regeneration, growth factors were delivered directly in the damaged renal tissues. The growth factors have included, among others, epidermal growth factor (EGF), transforming growth factor (TGF)[106] fibroblast growth factor (FGF).[107] *etc.* Later, biodegradable scaffolds that incorporated growth factors such as VEGF, FGF and platelet-derived growth factor-BB (PDGF-BB) were used to promote smooth muscle regeneration and accelerate neovascularization of the bladder.[108–111] Composites were made with poly-L-lactic acid (PLLA) combined with collagen obtained from de-cellularized matrices. These composite scaffolds with good mechanical properties facilitated cell attachment and growth.[112,113] The cell-free approach is ideal for bladder reconstruction, as this strategy is simple and does not require cell incorporation. With respect to the scaffolds, bladder acellular matrix (BAM) is widely used in bladder reconstruction. After implantation of BAM in a rabbit, the results showed that the regenerated bladder possessed similar histologic and functional properties to the native tissue.[112] The combination of a silk fibroin biolayer with BAM promoted vascularization and nerve regeneration.[113] In a study reported in 2016, various amounts of kidney-derived ECM were incorporated in poly(lactic-*co*-glycolic acid) (PLGA) scaffolds to evaluate kidney tissue regeneration in partially nephrectomised mice. The results indicated that scaffolds with just 10% ECM were effective for the regeneration of blood vessels and glomerulus. These results suggested that ECM can potentially be used in the treatment of kidney diseases such as AKI.[114]

5.2.2 Polymers. Several hybrid polymer hydrogels have been used for cell delivery to support kidney repair.[115,116] A hydrogel made with hyaluronic acid/collagen crosslinked with PEGDA was loaded with stromal cell-derived factor-1 (SDF-1).[117] When tested as a cell delivery system for endothelial progenitor cells (EPCs), the hydrogel appeared to protect the cells from cytotoxic insult. SDF-1 loaded in the hydrogel stimulated increased cell engraftment and proliferation in kidneys.[117,118] In a formation in which PLGA matrix was coated with $Mg(OH)_2$ and ECM, it was found that $Mg(OH)_2$ was able to prevent the acidic environment caused by the

decomposition of PLGA, leading to a reduced inflammatory effect. ECM favored cell attachment and proliferation.[119]

The use of nanofibers has also proved beneficial both for cell delivery and for kidney repair and regeneration. In one study, McManus *et al.* used electrospun fibrinogen mats to support human bladder smooth muscle cell (HBSM)-induced scaffold remodelling. *In vitro* studies demonstrated migration of cells into the scaffold and initiation of its remodelling through collagen deposition. These initial findings revealed the potential of electrospun fibrinogen for applications in urological tissue engineering.[120] Pokrywczynska *et al.* developed a five-layered poly(L-lactide-*co*-caprolactone) (PLC) nanofibrous membrane along with a small intestinal submucosa (SIS) membrane cultured with adipose-derived stem cells (ADSCs). The implanted scaffolds revealed the formation of various layers of a normal urinary bladder wall.[121] In another study, a polymer made with a nanomaterial was developed to treat IR-induced AKI and renal fibrosis. Poly(lactic-*co*-glycolic acid) (PLGA) NPs were loaded with Oltipraz (PLGA-Oltipraz NPs). The NPs displayed improved cell viability and had a stronger antioxidant effect. When AKI-affected mice were treated with PLGA-Oltipraz NPs, there was a reduction in collagen deposition and tubular necrosis, and improved renal function and renal fibrosis. These results demonstrated the potential of PLGA-Oltipraz NPs for the treatment of AKI and fibrosis.[122]

5.2.3 Extracellular matrix. AKI is also related to urethral damage leading to trauma, inflammation, blockage *etc*. Urethral reconstruction has been a challenge for many decades, even for skilled urologists. The factors that determine the type of urethroplasty include the structure length, its location, and the number of previous urethral surgeries. Urethral reconstruction is successful when no additional surgical interventions, such as optical urethrotomy or dilatation, are required. Classical approaches used for the treatment of severe urethral strictures include full-thickness skin grafts, vascularized skin flaps, buccal mucosa grafts, *etc*., with mixed results.[123] Acellular matrix proved to be a simple, effective and ideal biomaterial for urethral repair. In a study by Nuininga *et al.*, a cross-linked collagen and compressed collagen structure was used for the regeneration of urethral lesions in rabbits.[124] In another study, an injectable collagen-based hydrogel was administered into the kidney of animals with sustained ischemia/reperfusion injury, and the kidneys were examined after 4 weeks for host tissue response. Expression of renal stem/progenitor cell markers such as CD24, PAX-2 and CD133, as well as MSC marker in the infiltrating cells, indicated the regenerative potential of the hydrogel. The results showed that injectable collagen hydrogel promoted both the recruitment of host renal stem cells or progenitors, and the *in situ* regeneration of glomerular structures and renal tubules.[125] Many *in vivo* studies on mice as well as clinical trials have demonstrated successful urethral regeneration using these matrices.[126] In 1999, Chen *et al.* reported the first successful urethral reconstruction in rabbits using matrix grafts composed of porcine acellular bladder submucosa. Histological and radiographic analyses indicated its functionality, with the acellular matrices revealing a normal cellular organization that was indistinguishable from the native tissue.[127] In 2002, a study reported the use of a porcine small intestine submucosa (SIS) in urethral reconstruction in humans. Urethral patency was reported in all subjects at 6 months follow-up.[128] The results were further confirmed in a clinical trial using 40 subjects and reported good long-term results.[129] Human cadaveric acellular matrix grafts have been used for the last 10 years.[130,131] Fiala *et al.* and El Kassaby *et al.* demonstrated successful urethral reconstruction in humans (Fig. 5).[132,133] These encouraging data indicate that in the future both cell-seeded and cell-free biomaterials may be extensively used to promote tissue repair and regeneration.

5.3 Biomaterials for liver tissue engineering

The current COVID-19 pandemic, caused by SARS-CoV-2, has become a major public health crisis over the last 12 months. Recent reports and patient case studies have shown that about 2–11% of patients with COVID-19 also develop chronic liver disease. During the previous SARS epidemic, around 60% of patients were reported to develop chronic liver damage.[134] In the current pandemic, similar hepatic dysfunction has been observed in 14–53% of patients with severe COVID-19. Cases of acute liver injury have been confirmed by the liver function tests of COVID-19 patients, which included increased levels of alkaline phosphatase (ALP), aspartate, alanine aminotransferase (AAT), total bilirubin and gamma glutamyl transferase (GGT).[135,136] Previous studies have shown that the virus could be a cause of liver tumors, and many immunotherapy approaches have been used in an attempt to overcome the viral effects on liver tissue.[137] The severe prolonged hepatic effects observed in post-COVID-19 patients could be attributed to the direct cytopathic effect of the virus on liver cells. Other associated conditions, such as pneumonia-associated hypoxia, sepsis or drug-induced liver hepatoxicity, might also contribute to the chronic liver damage.[138] The ability of SARS-CoV-2 to infect the liver is due to the expression of ACE2 receptors found in cholangiocytes in the liver,[139] which indicates that the virus could directly bind to cholangiocytes and disrupt liver function.[134,138]

In view of the current pandemic, patients with liver disease need special attention and continuous follow-up. Hepatologists and transplant surgeons are still evaluating the implications of this disease.[140] Based on previous findings, tissue engineering can once again provide a valuable opportunity to induce liver tissue repair in subjects suffering from chronic liver damage as a consequence of SARS-CoV-2 infection. In this context, biomaterials that have previously given successful results in liver tissue regeneration can be used.

5.3.1 Extracellular matrix. The use of de-cellularized tissues and organs is evolving as a promising approach for application in tissue regeneration, in view of its ability to retain the native ECM matrix in addition to the preserved vascular integrity.[141,142] De-cellularized splenic scaffolds with a well-preserved 3D ultrastructure have been reported. These scaffolds displayed similar structures and had the same

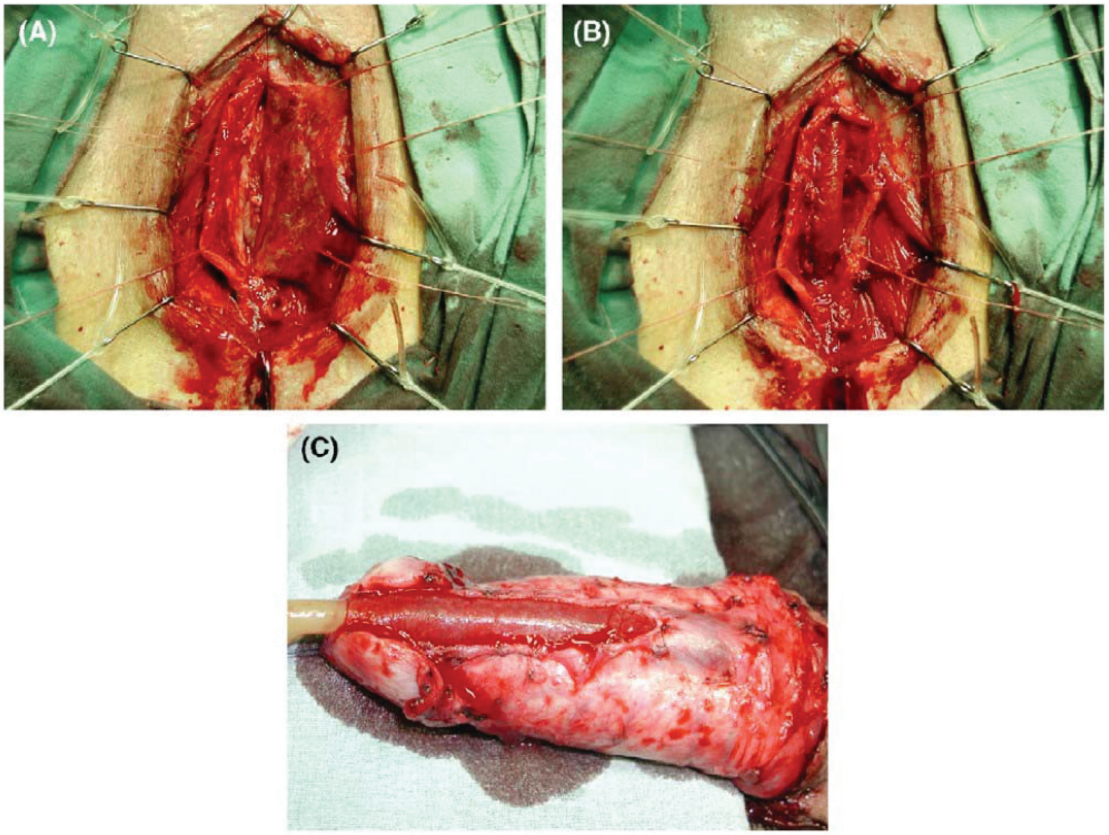

Fig. 5 (A) Urethral mucosa and SIS are anastomosed with a running suture; (B) SIS on lay patch is sutured in place without bulbar closure; (C) distal urethroplasty and meatoplasty. Reproduced from ref. 132 with permission from [Elsevier], copyright [2007].

mechanical properties as native liver tissue, indicating that they could be used as a liver substitute when liver donation is not feasible.[143,144] Uygun *et al.* used an antegrade perfusion method to develop the first de-cellularized whole-organ rodent liver, and obtained a translucent acellular tissue within a few days.[145] Successful decellularization of a human liver was performed using a novel retrograde two-step perfusion methodology. The de-cellularized organ was shown to retain the architecture, the 3D hepatic environment and the liver ECM (Fig. 6).[146] Baptista *et al.* demonstrated efficient differentiation of fetal hepatoblasts into hepatic and biliary lineages using decellularized matrix (Fig. 7).[147] The use of ECM has also proved to be another promising approach for tissue regeneration. The incorporation of lumican in a hydrogel matrix resulted in faster differentiation of HSCs into a myofibroblastic lineage.[148] ECM composition is reported to influence the fate of stem cells and progenitor cells. A combination of fibronectin and collagen IV facilitated the differentiation of cholangiogenic cells into liver progenitor cells.[149] The use of human liver progenitor-derived acellular matrix resulted in hepatic commitment of induced pluripotent stem cells (iPSC).[150] Ogiso *et al.* showed that in the absence of pro-differentiation signals, organ-specific cell-derived ECM alone could promote the maturation of engrafted fetal hepatocytes into hepatic and biliary lineages.[151] Co-culture liver systems developed with microfluidic confinement using porcine liver-derived collagen hydrogels expressed liver-specific markers such as CYP3A4, CYP2C9 and glucuronidation activities in the cultures.[152,153]

Vyas *et al.* used acellular liver ECM scaffolds to culture fetal liver cells, and showed the formation of complex hepatobiliary organoid structures *in vitro*.[154] Several other studies also used Matrigel to develop similar liver organoids.[155,156]

5.3.2 Polymers. Apart from ECM, various natural polymers, such as alginate, cellulose, *etc.*, and synthetic polymers such as poly(vinyl alcohol) (PVA), poly(L-lactic acid) (PLLA), polyethylene glycol (PEG), poly(*N*-isopropylacrylamide), polycaprolactone (PCL) and poly(lactic-*co*-glycolic acid) (PLGA) have also been used.[157,158] In one such study, HepaRG cells were cultured in various commercial hydrogels, such as ExtraCel, MaxGel, *etc.*, and were then compared with collagen hydrogel.[159] Another study demonstrated the potential of a macroporous alginate scaffold to significantly improve the differentiation and maturation of newborn liver cells compared with a collagen scaffold.[160] An implanted alginate scaffold in partially hepatectomized mice showed improved survival compared with the untreated group.[161] Porous sponges composed of a combination of alginate and galactosylated chitosan (AL-GC) promoted hepatocyte growth to a greater extent than alginate sponge due to the presence of the asialoglycoprotein receptor (ASGPR), a ligand specific to hepatocytes. Hepatocytes cultured

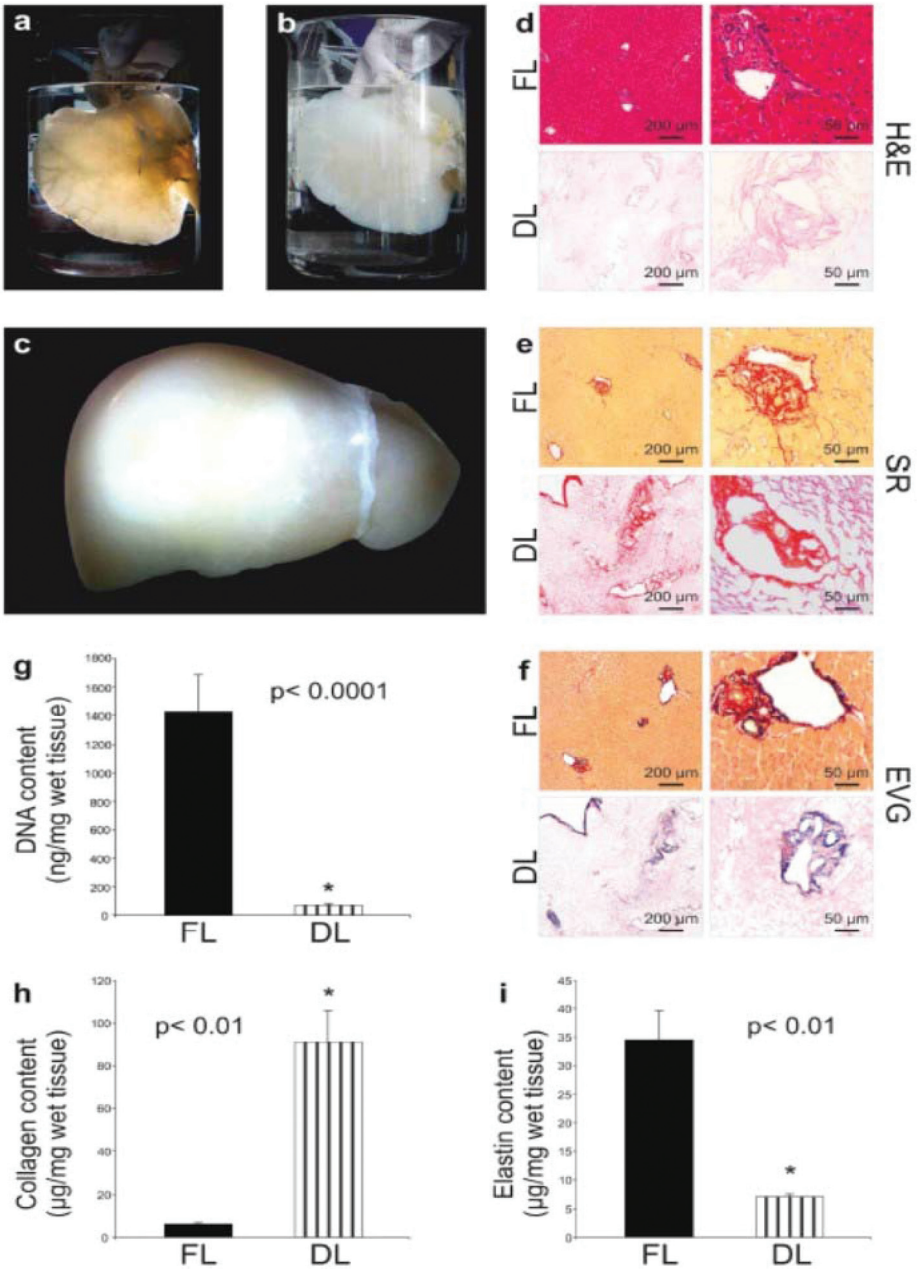

Fig. 6 Perfusion–decellularization of human liver. Macroscopic appearance of a decellularized left lobe showing preservation of the vascular tree (a), translucent color (b) and a complete human liver (c). Histological comparison (10× and 40× magnification, left panel and right panel, respectively) of fresh liver (FL) and decellularized liver (DL) by Hematoxylin and eosin (H&E) (d), Sirius red (SR) (e) and Elastin Von Gieson EVG (f) staining demonstrating removal of cells and preservation of collagen and elastin in DL. Scale bar for 10× magnification: 200 μm and 40×: 50 μm. DNA quantification demonstrated significant DNA reduction from 1425.23 (g). Collagen significantly increased from 5.860726 ± 1.417547 μg mg^{-1} in FL to 90.85345 ± 14.16523 μg mg^{-1} in DL scaffolds (h). Elastin quantification demonstrated a significant decrease from 34.56827 ± 5.102387 μg mg^{-1} to 7.073619 ± 0.434233 μg mg^{-1} in DL scaffolds (i). Reproduced from ref. 146 with permission from [Nature], copyright [2015].

in AL-GC foams formed large cell aggregates, expressed connexin-32 and E-cadherin as markers for cell–cell contact, and showed enhanced liver-specific functions.[162]

As well as these natural polymers, many synthetic polymers are also used. In one study, Hayward *et al.* developed a galactose-functionalized polyHIPE hydrogel for routine hepatocyte culture.[163] PLLA–PLGA-based biomaterials used in a flow bioreactor promoted spheroid formations of human and rat hepatocytes. Such pre-cultured rat hepatocytes, when transplanted, showed initial cell loss but regained 100% of their cell mass within 6 months when implanted in syngeneic rats.[164] Kasuya *et al.* demonstrated the use of PLGA membranes for the culture of hepatocytes, which improved the liver-specific functions compared with monolayer culture.[165] The PCL scaffolds modified with galactosylated chitosan exhibited improved hepatic functionality over a period of 7 days.[166] In another

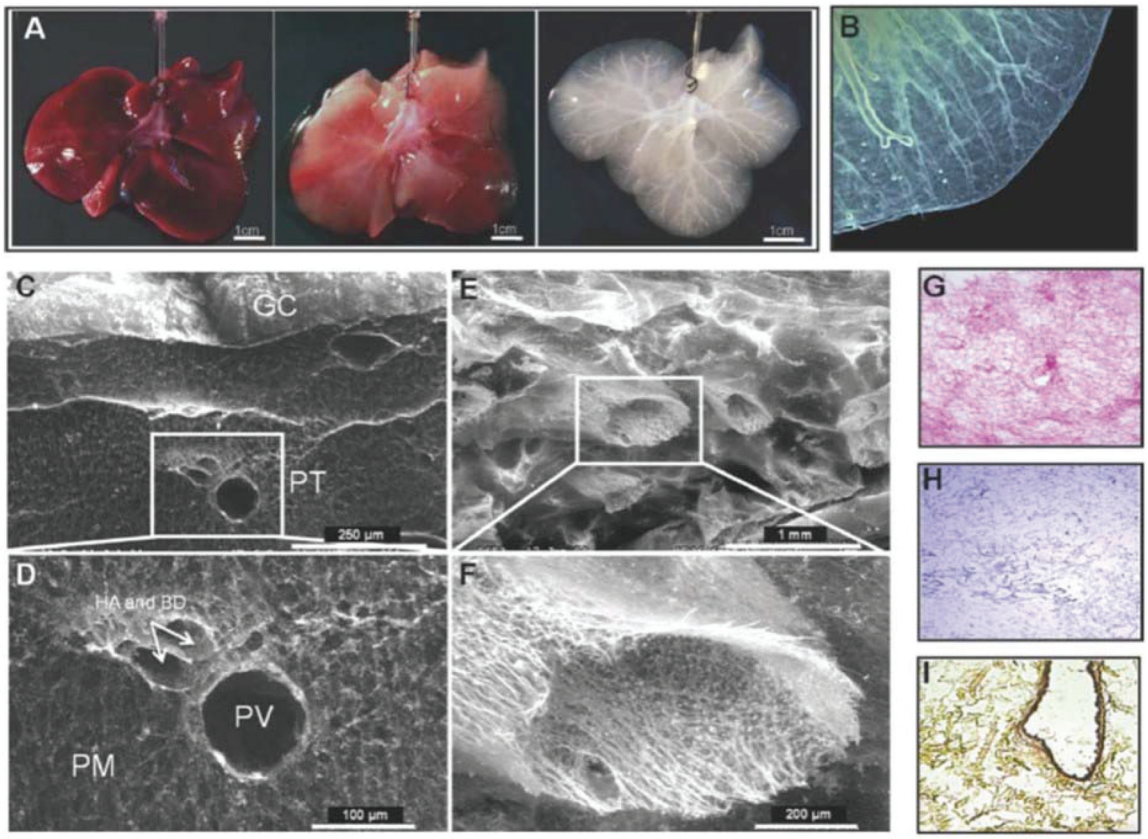

Fig. 7 Preparation and ultrastructural analysis of the acellular vascularized bioscaffold. Whole ferret livers were decellularized as described under "Methods". (A) Macroscopic view of a ferret liver at 0, 20, and 120 minutes of the decellularization process. (B) A decellularized lobe of the liver demonstrating clear parenchyma, defined liver capsule and vasculature. (C) Scanning electron microscopy (SEM) image of a cross-section of the decellularized bioscaffold at 120× magnification showing an intact Glisson's capsule (GC), intact lobules and vascular structures of the portal triad (PT) (see cartoon in Fig. 4A). (D) A higher magnification image of C demonstrating intact 'portal triad' with portal vein (PV), hepatic artery (HA) and biliary duct (BD), and parenchymal matrix mesh (PM). (E) SEM image of a cross-section of the liver bioscaffold at the liver hilum at 40× magnification showing blood vessels constructed of woven collagen fibers and no cellular material visualized. (F) A higher-magnification image of (E) further demonstrates the details of a woven structure of a blood vessel. (G) H&E staining of decellularized liver sections showing no cellular staining and pink eosinophilic staining expected from proteinous extracellular matrix. (H) Mason's trichrome staining of decellularized liver sections shows blue staining indicative of extracellular matrix proteins without any cellular material observed. (I) Movat-Pentachrome staining of decellularized liver sections demonstrates yellow staining for collagen with periarteriole dark staining for elastin. Reproduced from ref. 147 with permission from [Wiley], copyright [2011].

approach, an *in situ* photo-polymerized cell-laden PEG-based hydrogel was used for the construction of micro tissue structures. When hepatocytes were suspended in a pre-polymer solution and photo-immobilized locally, it supported the formation of functional 3D hepatic constructs with complex internal features.[167] Methods such as electrospinning and nano-imprint lithography have been used for the formation of nanofibers, nanopillars which have been used to control cell shape, and for suitable cell–cell interactions. Cell shape transitions have been observed when cultured on these nanopatterned substrates.[168,169]

Hybrid polymeric biomaterials are also used to promote hepatic tissue regeneration. The adhesion peptides RGD and YIGSR enhanced the attachment of hepatocytes on PCL and PLA surfaces compared with pure polymers.[170] A hydrogel was developed by Lee *et al.* using poly(ethylene glycol) diacrylate (PEGDA)/hyaluronic acid, and was coated with the synthetic peptide Gly-Arg-Gly-Asp-Ser (GRGDS). The differentiation of hepatocytes was observed on this hydrogel for 16 days.[171] Using a 3D sandwich culture with GRGDS-modified polyethylene terephthalate (PET) on the top and galactosylated PET as the bottom layer, with hepatocytes sandwiched in between, the cells were reported to maintain their functional state for a period of 14 days. This model was shown to be superior to conventional sandwich collagen cultures.[172] A thermosensitive hydrogel made with poly(ethylene glycol)-*b*-poly(L-alanine) supported efficient hepatogenic differentiation of tonsil-derived mesenchymal stem cells.[173]

5.4 Biomaterials for neurological tissue engineering

COVID-19 is also associated with a range of neurological disorders, including headache, anosmia, impaired consciousness, loss of smell and taste, and stroke.[174,175] A growing number of case reports and brain imaging data describe a wide array of

neurological manifestations in COVID-19 patients.[176] The common clinical features include anosmia, ageusia, ischemic stroke, intracranial hemorrhage, hypoxic-ischemic encephalopathy, encephalitis, and acute hemorrhagic necrotizing encephalopathy.[177] Many reports have shown that patients with severe COVID-19 can have a cytokine storm syndrome which may lead to ischemic strokes.[178] MRI scans showed that 47% of patients had acute neuroimaging abnormalities, which included acute ischemic infarcts (31%), intracranial hemorrhage (6%), multiple sclerosis (MS), plaque exacerbation (10%), cerebral venous thrombosis (12%), Guillian-Barre syndrome, nonspecific encephalopathy (10%), Miller–Fisher syndrome (10%) and posterior reversible encephalopathy syndrome (PRES) (5%).[176] COVID-19 patients with encephalopathy have been reported in Wuhan, China and in France.[179] In one of these reports Helms *et al.* described neurological complications in a case study where 58 patients were suffering from ARSD due to COVID-19 and were admitted to the ICU in France between 3 March 2020 and 3 April 2020. Some of the common neurological symptoms observed in these patients post discharge include agitation, confusion, hyperreflexia, encephalopathy and dysexecutive syndrome.[177,180] The study report showed that the virus can cause inflammation of brain tissue and can lead to cell damage, leading to a number of disorders.[181,182] Considering these neurological manifestations, it is believed that biomaterials can provide an opportunity to prevent further damage to the brain cells and thus prevent shock and other disorders.

5.4.1 Extracellular matrix. These biomaterials are widely used for soft tissue regeneration due to their biocompatibility and their mechanical properties.[183,184] To provide an optimal growth-promoting environment for axonal tissue regeneration, the physical, chemical and biochemical properties of the scaffold must be designed in a way that provides guidance cues to allow substrate remodeling and support the axons that cross the lesion site.[185] The most commonly used natural hydrogels in neural tissue engineering are collagen[186,187] and hyaluronic acid (HA).[188,189] Many reports have shown that collagen scaffolds that incorporate nerve growth factor are capable of improving cell viability *in vitro*.[190] Neurons cultured in collagen hydrogels have the ability to generate spontaneous synaptic potentials.[191] Modification of HA hydrogels with polylysine, homopolypeptides and anti-NgR (an inhibitor of the Nogocomplex myelin-associated proteins)[188,192] resulted in increased regenerative capacity of the brain tissue. Improvement in neural progenitor cell attachment and neuron-like morphology was observed in primary hippocampal cells. An HA hydrogel immobilized with argenine–glysine–aspartate (RGD) peptides/laminin and implanted into rat cortex lesions resulted in improved angiogenesis and neurite extension with minimal glial scarring.[193,194] Regeneration after peripheral nerve injury has been achieved using an injectable chitosan/HA hydrogel.[195] Fibrin hydrogels also show improved cell attachment, migration and proliferation of brain cells, and good neural recovery,[196] and with delayed reactive astrocyte recruitment and enhanced neuronal migration.[197] Neuronal cell attachment and growth was observed to increase by 15-fold in chitosan–agarose-blended hydrogels.[198] *In vitro*, Matrigel seeded with a co-culture of neurons and astrocytes promoted the expression of mature neuron-specific cytoskeletal proteins and produced a network of functional synapses.[199]

Several synthetic hydrogels, such as poly(*N*-2-(hydroxypropyl) methacrylamide) (pHPMA), polyethylene glycol (PEG)[200] and poly(hydroxyethylmethacrylate) (pHEMA),[201] have been used for tissue repair after brain injury.[202] These hydrogels were used to enable recovery from traumatic brain injury (TBI). When the hydrogels were implanted into cortical lesion cavities, growth of axons and astrocytes was observed in both hydrogels.[200] A photopolymerized hydrogel that had a polylysine backbone with linear PEG branches supported the proliferation of neural progenitor cells *in* vitro, and also differentiation into mature neurons.[203] A hydrogel composed of pHEMA was capable of guiding neurite outgrowth, and could be used in CNS or PNS repair.[204] Furthermore, a hybrid hydrogel comprising a mixture of HA and a biodegradable synthetic polymer, such as poly-L-lysine and PLGA, showed great potential for controlled drug delivery at the site of axonal regrowth after injury in both *in vitro*[205] and *in vivo* studies.[206] Researchers used poly(lactide-*co*-glycolide) copolymer (PLGA) fiber as a scaffold which supported the formation of brain organoid and induced cortical plate formation similar to that in human brain.[207] However, to overcome the limitation of vascularization, Mansour *et al.* developed a functional and vascularized brain model on a Matrigel which on transplantation showed neuronal maturation and differentiation, microglial incorporation and axonal growth in multiple host mouse brain regions.[208]

Another form of hydrogel which is used as a scaffold in brain tissue engineering is the self-assembling peptide nanofibre scaffold (SAPNS). These hydrogels are composed of various amphiphilic molecules or oligopeptides that spontaneously form fibrillar networks in the presence of trigger conditions.[209] The two types of polymer peptides reported in neural tissue engineering are arginine–alanine–aspartate–alanine (RADA)16-I and isoleucine–lysine–valine–alanine–valine (IKVAV). IKVAV has been reported to selectively induce the differentiation of encapsulated neural progenitor cells into neurons while downregulating astrocyte differentiation.[210,211] RADA16-I has been shown to support neuronal cell survival, differentiation and neurite outgrowth, and to induce functional synapse formation with no immunogenic response.[212] Histological analysis of the brain injury sites post SAPNS application showed fewer macrophages and astrocytes, indicating its immunocompatibility compared with the control exhibiting secondary tissue loss.[213]

5.4.2 Polymers. Natural polymers used in neural tissue engineering include extracellular matrix (ECM) components such as collagen, and polymers such as alginate, chitosan and even silk. Natural polymers are the most efficient type of polymer used in neural tissue engineering, and they have been preclinically studied in numerous animal models, including primates.[214] Among them, collagen is the most prominent bio-

material used in neural tissue engineering. A small (5 mm) nerve gap in non-human primates treated with a collagen-based nerve guide was observed to recover with physiological resemblance to a graft-induced repair.[215,216] Conduits prepared with collagen and tested as an internal filler to induce regeneration of peripheral nerve lesions with a gap of more than 15 mm in a rat sciatic nerve injury model displayed regeneration.[217] NeuraGen® and Neuromaix® are the two collagen-based biomaterials that are currently approved for clinical testing for neural tissue regeneration, and they have shown good results in 43% of patients (Fig. 8).[218,219] The use of silk fibroin has also shown effective results in neural tissue regeneration. Benfenati *et al.* used silk fibroin to induce neurite outgrowth and neuronal functions.[220] In another study, Gennari *et al.* developed a silk fibroin for *in situ* delivery of allopregnanolone (ALLO) and gamma-aminobutyric acid (GABA), and it showed strong attachment of Schwann cells and neuronal survival.[221] In addition, chitosan has been successfully used in neural tissue engineering, exhibiting cell attachment, cell interaction, cell survival, and neuronal outgrowth.[222,223] Synthetic polymers are also used in neural TE which includes poly(α-hydroxy acid) polymers such as PLA, PGA, and their copolymers (PLGA) *etc*. PLGA and PLA have been efficiently used to design scaffolds that provide support for Schwann cells, have a synergistic effect on neural regeneration, allow elongation of axons, and also promote vascular growth.[184,224,225] Another synthetic polymer that is widely used is PEG, which has also been reported to improve neural cell survival, growth and differentiation in CNS injuries.[226,227]

Hybrid polymers have had an important role in neural tissue repair. One example is the polymer conduit composed

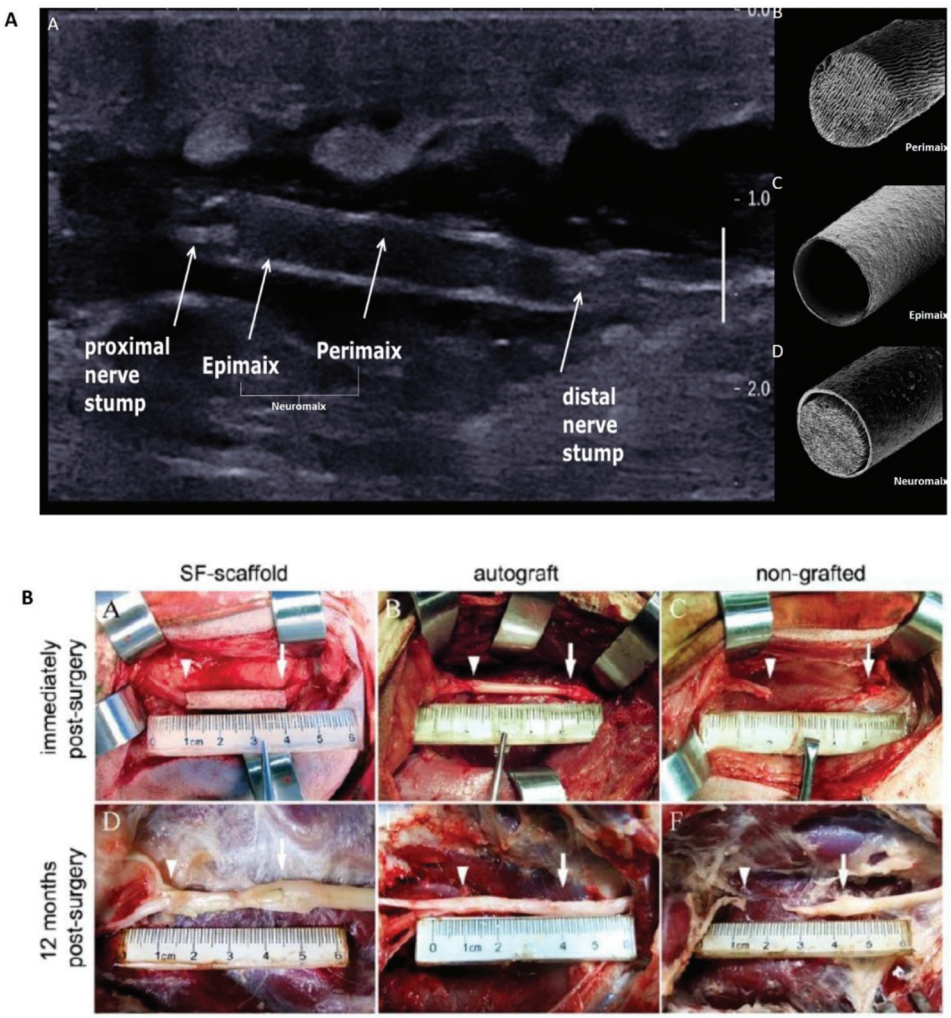

Fig. 8 (A) Example of a high-resolution ultrasound image of Neuromaix 1 month after implantation in the SN biopsy gap. Neuromaix, consisting of Epimaix and Perimaix, was clearly detectable between the proximal and distal nerve stumps 1 month after implantation in the SN biopsy gap (example of patient 001; scale bar: 5 mm). At the right SEM images of the Neuromaix nerve guide. Reproduced from ref. 219 with permission from [Springer Nature], copyright [2017]. (B) Gross view obtained from dogs immediately (A–C) and 12 months (B–F) post surgery in SF-based neural scaffold (A and D), autograft (B and E) and non-grafted (C and F) groups. The proximal and distal coaptations are indicated by an arrow and an arrowhead, respectively. Minimal scale: 1 mm. Reproduced from ref. 240 with permission from [Wiley], copyright [2018].

of PCL/gelatin. Gelatin combined with PCL supported both neurite outgrowth and the proliferation of Schwann cells *in vitro*.[228–230] In another study a PCL/collagen hybrid scaffold that incorporated a gelatin matrix was used to reconstruct a 15 mm gap in sciatic nerve in rats.[231] Other research found that PCL/chitosan fibres supported PC12 cell attachment and proliferation, enhancing neurite extension along the fibre orientation.[232] PLGA/chitosan scaffolds showed neuronal differentiation both *in vitro* and *in vivo* for peripheral nerve regeneration.[233,234] In another study Liu *et al.* used a hybrid polymer composed of PLGA/PEG which showed enhanced cell migration and growth along with improved functional recovery in rats.[235] Yang *et al.* developed another biodegradable hybrid consisting of gelatin crosslinked with genipin and tri-calcium phosphate ceramic particles for peripheral nerve regeneration.[236]

Nanofibers are also used in neural TE. Gelatin electrospun nanofibers have been found to support the differentiation of motor neuron-like cells, demonstrating their potential in CNS applications.[237] Recently, electrospun PLA/silk fibroin nanofibres were incorporated with nerve growth factor (NGF) which supported the attachment and differentiation of PC12 cells.[238] A silk-based electrospun nerve conduit was developed by Dinis *et al.* for peripheral nerve regeneration.[239] As shown in Fig. 8, Xue *et al.* successfully demonstrated the use of electrospun silk–fibroin scaffold in the regeneration of a 30 mm long sciatic nerve lesion in dogs.[240]

Recently, the potential use of conducting and semi-conducting materials in neural tissue regeneration has been widely investigated, as these materials can induce signal transfer and serve as metallic microelectrodes. Commonly used conducting polymers include polypyrrole (PPY) and PANI, both of which support the development and regeneration of nerve tissue.[241–243] Composites containing PPY/HA and PPY/collagen fibres, respectively, showed improved neural adhesion, proliferation and growth.[244,245] Similarly, scaffolds composed of poly(3,4-ethylene dioxythiophene) (PEDOT)/chitosan/gelatin showed improved neurogenesis and cell growth and attachment.[246]

6 Conclusion

The ongoing pandemic has caused significant mortality and had a huge social, economic and health impact on society. Researchers are in pursuit of highly effective drugs/vaccines to treat/prevent the virus, with mixed success. Moreover, the detrimental effects of the virus on multiple organs in COVID patients, resulting in tissue damage and organ failure, are a major cause of concern. Biomaterials can be used to stop or even reverse the effects of virus-induced tissue damage by serving as a scaffold for growth of cells and thereby facilitating the process of tissue repair. With ample literature evidence, this review has provided the multiple prospects of biomaterials in the repair of various tissues and organs. Since the ability of many of these biomaterials to repair tissues and organs that are susceptible to SARS-CoV-2 has already been demonstrated, these applications can now be further explored in relevant models of injury. Given the ongoing pandemic, with no clear prospect of treatment in sight, there is an urgent need to develop strategies to address the growing number of COVID-19 patients with tissue and organ damage caused by the virus. Tissue engineering using biomaterials as scaffolds appears to be a promising approach to overcome this problem.

7 Future prospects

With the world experiencing a second wave of SARS-CoV-2 infections, there is no evidence that the pandemic will end soon. Despite promising reports on the development of multiple vaccines to prevent infection, 100% success is yet to be achieved. In addition, the high demand, stability issues, high cost, and massive logistics involved in vaccinating the world's population mean that even with the vaccine rollout the virus would continue to infect a significant number of people. Furthermore, it is not clear if the vaccine-induced immunity is long term. According to some case reports, the incidence of relapse in some infected patients suggests that the life cycle of the virus in the host is uncertain. While our understanding of COVID-19 is evolving, and numerous vaccines are being developed, it is certain that infected patients with damaged organs require immediate attention. Approaches to for inducing early repair or regeneration of the damaged tissues or organs can prevent their further deterioration. With multiple studies both of animal models and of human subjects having demonstrated the positive role of biomaterials in tissue regeneration, this can be explored further in human subjects to evaluate its efficacy. Moreover, these biomaterials can be further exploited in many other new emerging technologies, such as 3D bioprinting in organ-on-a-chip systems, for supporting tissue regeneration. Such techniques can be used in the formation of 3D simulation models of organs to study the process of virus entry, replication and its effect on the cellular components. With advances in biomaterials processing for developing functional tissue/organ substitutes, the possibility of achieving regeneration of tissues that are hard to heal is becoming a reality.

Abbreviations

SARS	Severe acute respiratory syndrome
MERS	Middle East respiratory syndrome
ARDS	Acute respiratory distress syndrome
RBD	Receptor-binding domain
ACE2	Angiotensin converting enzyme 2
ECMO	Extracorporeal membrane oxygenation
PVA	Polyvinyl alcohol
PET	Polyethylene terephthalate
PU	Polyurethane
COPD	Chronic obstructive pulmonary disease

VEGF	Vascular endothelial growth factor
HA	Hyaluronic acid
HEMA	Hydroxyethyl methacrylate
PCL	Poly(ε-caprolactone)
AKI	Acute kidney injury
CKD	Chronic kidney disease
ECM	Extracellular matrix components
EGF	Epidermal growth factor
TGF	Transforming growth factor
PLLA	Poly-L-lactic acid
BAM	Bladder acellular matrices
EPCs	Endothelial progenitor cells
iPSC	Induced pluripotent stem cells
SDF-1	Stromal cell-derived factor-1
TBM	Tracheobronchomalacia
MLE-12	Murine lung epithelial cells
FGF	Fibroblast growth factor
PDGF-BB	Platelet-derived growth factor-BB
PLLA	Poly-L-lactic acid
PLGA	Poly(lactic-*co*-glycolic acid)
PEGDA	Poly (ethylene glycol) diacrylate
EPCs	Endothelial progenitor cells
HBSM	Human bladder smooth muscle cells
SIS	Small intestine submucosa
UAMG	Urethral acellular matrix grafts
ALP	Alkaline phosphatase
AAT	Aspartate, alanine aminotransferase
GGT	Gamma glutamyl transferase
GABA	Gamma-aminobutyric acid
ASGPR	Asialoglycoprotein receptor
PRES	Posterior reversible encephalopathy syndrome
NGF	Nerve growth factor
TBI	Traumatic brain injury
SAPNS	Self-assembling peptide nanofibre scaffold
ESCs	Embryonic stem cells
iPSCs	Induced pluripotent stem cells

Author contributions

Himadri Roy: Conceptualization and writing. Rupali Singh: Writing - Original draft preparation. Deepa Ghosh: Writing - Reviewing and editing.

Conflicts of interest

The authors declare no conflicts of interest.

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References

1 H. A. Rothan and S. N. Byrareddy, *J. Autoimmun.*, 2020, **109**, 102433.
2 C. Sohrabi, Z. Alsafi, N. O'Neill, M. Khan, A. Kerwan, A. Al-Jabir, C. Iosifidis and R. Agha, *Int. J. Surg.*, 2020, **76**, 71–76.
3 B. Shanmugaraj, A. Malla and W. Phoolcharoen, *Pathogens*, 2020, **9**, 148.
4 D. S. Hui, E. I. Azhar, T. A. Madani, F. Ntoumi, R. Kock, O. Dar, G. Ippolito, T. D. Mchugh, Z. A. Memish, C. Drosten, A. Zumla and E. Petersen, *Int. J. Infect. Dis.*, 2020, **91**, 264–266.
5 T. S. Marcus, J. Heese, A. Scheibe, S. Shelly, S. X. Lalla and J. F. Hugo, *Harm Reduct. J.*, 2020, **17**, 60.
6 WHO Coronavirus Disease (COVID-19) Dashboard, https://covid19.who.int, (accessed September 6, 2020).
7 M. A. Shereen, S. Khan, A. Kazmi, N. Bashir and R. Siddique, *J. Adv. Res.*, 2020, **24**, 91–98.
8 Y. Liu, A. A. Gayle, A. Wilder-Smith and J. Rocklöv, *J. Travel Med.*, 2020, **27**, taaa021.
9 N. Chen, M. Zhou, X. Dong, J. Qu, F. Gong, Y. Han, Y. Qiu, J. Wang, Y. Liu, Y. Wei, J. Xia, T. Yu, X. Zhang and L. Zhang, *Lancet*, 2020, **395**, 507–513.
10 D. Wang, B. Hu, C. Hu, F. Zhu, X. Liu, J. Zhang, B. Wang, H. Xiang, Z. Cheng, Y. Xiong, Y. Zhao, Y. Li, X. Wang and Z. Peng, *J. Am. Med. Assoc.*, 2020, **323**, 1061–1069.
11 Z. Tang, N. Kong, X. Zhang, Y. Liu, P. Hu, S. Mou, P. Liljeström, J. Shi, W. Tan, J. S. Kim, Y. Cao, R. Langer, K. W. Leong, O. C. Farokhzad and W. Tao, *Nat. Rev. Mater.*, 2020, **5**, 847–860.
12 Z. Zhang, Z. Tang, N. Farokhzad, T. Chen and W. Tao, *Matter*, 2020, **3**, 1818–1820.
13 Z. Tang, X. Zhang, Y. Shu, M. Guo, H. Zhang and W. Tao, *Nano Today*, 2021, **36**, 101019.
14 J. F.-W. Chan, K. K.-W. To, H. Tse, D.-Y. Jin and K.-Y. Yuen, *Trends Microbiol.*, 2013, **21**, 544–555.
15 M. S. Majumder and K. D. Mandl, *Soc. Sci. Res.*, 2020, **24**, 3524675.
16 D. Wrapp, N. Wang, K. S. Corbett, J. A. Goldsmith, C.-L. Hsieh, O. Abiona, B. S. Graham and J. S. McLellan, *Science*, 2020, **367**, 1260–1263.
17 P. K. S. Chan, J. W. Tang and D. S. C. Hui, *Clin. Sci.*, 2006, **110**(2), 193–204.
18 C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, L. Zhang, G. Fan, J. Xu, X. Gu, Z. Cheng, T. Yu, J. Xia, Y. Wei, W. Wu, X. Xie, W. Yin, H. Li, M. Liu, Y. Xiao, H. Gao, L. Guo, J. Xie, G. Wang, R. Jiang, Z. Gao, Q. Jin, J. Wang and B. Cao, *Lancet*, 2020, **395**, 497–506.
19 A.-2019-nCoV Volunteers, Z. Li, M. Wu, J. Yao, J. Guo, X. Liao, S. Song, J. Li, G. Duan, Y. Zhou, X. Wu, Z. Zhou, T. Wang, M. Hu, X. Chen, Y. Fu, C. Lei, H. Dong, C. Xu,

Y. Hu, M. Han, Y. Zhou, H. Jia, X. Chen and J. Yan, *medRxiv*, 2020, DOI: 10.1101/2020.02.08.20021212.
20 T. Ai, Z. Yang, H. Hou, C. Zhan, C. Chen, W. Lv, Q. Tao, Z. Sun and L. Xia, *Radiology*, 2020, **296**, E32–E40.
21 Y. Zhao, Z. Zhao, Y. Wang, Y. Zhou, Y. Ma and W. Zuo, *Am. J. Respir. Crit. Care Med.*, 2020, **202**, 756–759.
22 M. Hoffmann, H. Kleine-Weber, S. Schroeder, N. Krüger, T. Herrler, S. Erichsen, T. S. Schiergens, G. Herrler, N.-H. Wu, A. Nitsche, M. A. Müller, C. Drosten and S. Pöhlmann, *Cell*, 2020, **181**(2), 271–280.e8.
23 E. Ruiz-Hitzky, M. Darder, B. Wicklein, C. Ruiz-Garcia, R. Martín-Sampedro, G. del Real and P. Aranda, *Adv. Healthcare Mater.*, 2020, **9**, 2000979.
24 F.-Y. Chang, H.-C. Chen, P.-J. Chen, M.-S. Ho, S.-L. Hsieh, J.-C. Lin, F.-T. Liu and H.-K. Sytwu, *J. Biomed. Sci.*, 2020, **27**, 72.
25 Y. Shi, Y. Wang, C. Shao, J. Huang, J. Gan, X. Huang, E. Bucci, M. Piacentini, G. Ippolito and G. Melino, *Cell Death Differ.*, 2020, **27**, 1451–1454.
26 M. Heidarpour, M. Vakhshoori, S. Abbasi, D. Shafie and N. Rezaei, *J. Med. Case Rep.*, 2020, **14**, 134.
27 C. Castells-Sala, M. Alemany-Ribes, T. Fernández-Muiños, L. Recha-Sancho, P. López-Chicón, C. Aloy-Reverté, J. Caballero-Camino, A. Márquez-Gil and C. E. Semino, *J. Biochips Tissue Chips*, 2013, 1.
28 Z. Wu and J. M. McGoogan, *J. Am. Med. Assoc.*, 2020, **323**, 1239.
29 G. Lemon, M. L. Lim, F. Ajalloueian and P. Macchiarini, *Br. Med. Bull.*, 2014, **110**, 35–45.
30 D. Sokocevic, N. R. Bonenfant, D. E. Wagner, Z. D. Borg, M. J. Lathrop, Y. W. Lam, B. Deng, M. J. DeSarno, T. Ashikaga, R. Loi, A. M. Hoffman and D. J. Weiss, *Biomaterials*, 2013, **34**, 3256–3269.
31 C. F. Andrade, A. P. Wong, T. K. Waddell, S. Keshavjee and M. Liu, *Am. J. Physiol.: Lung Cell. Mol. Physiol.*, 2007, **292**, L510–L518.
32 T. Tsuchiya, T. Obata, G. Hatachi and T. Nagayasu, *Front. Bioeng. Biotechnol.*, 2020, **8**, 105.
33 S. E. Dunphy, J. A. J. Bratt, K. M. Akram, N. R. Forsyth and A. J. El Haj, *J. Mech. Behav. Biomed. Mater.*, 2014, **38**, 251–259.
34 A. Abalymov, B. Parakhonskiy and A. G. Skirtach, *Polymers*, 2020, **12**, 620.
35 E. Biazar, *Polym. Adv. Technol.*, 2016, **27**, 1404–1412.
36 P. I. Lelkes, M. Li, A. Perets, M. J. Mondrinos, Y. Guo, X. Chen, A. G. MacDiarmid, F. K. Ko, C. M. Finck and Y. Wei, *Experimental analysis of nano and engineering materials and structures*, Springer, 2007, pp. 831–832.
37 A. Fakhari and C. Berkland, *Acta Biomater.*, 2013, **9**, 7081–7092.
38 Q. Chen, S. Liang and G. A. Thouas, *Prog. Polym. Sci.*, 2013, **38**, 584–671.
39 Y. Wang, G. A. Ameer, B. J. Sheppard and R. Langer, *Nat. Biotechnol.*, 2002, **20**, 602–606.
40 H. T. Aiyelabegan, S. S. Z. Zaidi, S. Fanuel, A. Eatemadi, M. T. K. Ebadi and E. Sadroddiny, *Int. J. Polym. Mater. Polym. Biomater.*, 2016, **65**, 853–861.
41 H. Zhang, C. Liang, X. Hou, L. Wang and D. Zhang, *Int. J. Nanomed.*, 2016, **11**, 1039–1050.
42 H. Sugihara, S. Toda, S. Miyabara, C. Fujiyama and N. Yonemitsu, *Am. J. Pathol.*, 1993, **142**, 783–792.
43 S. C. Pageau, O. V. Sazonova, J. Y. Wong, A. M. Soto and C. Sonnenschein, *Biomaterials*, 2011, **32**, 7169–7180.
44 P. Chen, E. Marsilio, R. H. Goldstein, I. V. Yannas and M. Spector, *Tissue Eng.*, 2005, **11**, 1436–1448.
45 M. Risbud, M. Endres, J. Ringe, R. Bhonde and M. Sittinger, *J. Biomed. Mater. Res.*, 2001, **56**, 120–127.
46 J. L. Young and A. J. Engler, *Biomaterials*, 2011, **32**, 1002–1009.
47 J. M. Leung, M. Niikura, C. W. T. Yang and D. D. Sin, *Eur. Respir. J.*, 2020, **56**, 2002108.
48 COVID-19 and COPD, https://www.medicalnewstoday.com/articles/covid-19-and-copd, (accessed September 6, 2020).
49 N. F. Voelkel, I. S. Douglas and M. Nicolls, *Chest*, 2007, **131**, 874–879.
50 T. Mammoto and A. Mammoto, *J. Visualized Exp.*, 2014, e52012.
51 R. Chetambath, *Lung India*, 2016, **33**(4), 451–452.
52 D. A. Zopf, S. J. Hollister, M. E. Nelson, R. G. Ohye and G. E. Green, *N. Engl. J. Med.*, 2013, **368**, 2043–2045.
53 R. J. Morrison, S. J. Hollister, M. F. Niedner, M. G. Mahani, A. H. Park, D. K. Mehta, R. G. Ohye and G. E. Green, *Sci. Transl. Med.*, 2015, **7**, 285ra64.
54 D. A. Zopf, C. L. Flanagan, M. Wheeler, S. J. Hollister and G. E. Green, *JAMA Otolaryngol.–Head Neck Surg.*, 2014, **140**, 66–71.
55 J. Cortiella, J. E. Nichols, K. Kojima, L. J. Bonassar, P. Dargon, A. K. Roy, M. P. Vacant, J. A. Niles and C. A. Vacanti, *Tissue Eng.*, 2006, **12**, 1213–1225.
56 H. Harrington, P. Cato, F. Salazar, M. Wilkinson, A. Knox, J. W. Haycock, F. Rose, J. W. Aylott and A. M. Ghaemmaghami, *Mol. Pharm.*, 2014, **11**, 2082–2091.
57 C. Radhakumary, A. M. Nandkumar and P. D. Nair, *Carbohydr. Polym.*, 2011, **85**, 439–445.
58 D. Singh, S. M. Zo, A. Kumar and S. S. Han, *J. Biomater. Sci., Polym. Ed.*, 2013, **24**, 1343–1359.
59 A. D. Augst, H. J. Kong and D. J. Mooney, *Macromol. Biosci.*, 2006, **6**, 623–633.
60 A. Tripathi and A. Kumar, *Macromol. Biosci.*, 2011, **11**, 22–35.
61 A. Kosmala, M. Fitzgerald, E. Moore and F. Stam, *Anal. Lett.*, 2017, **50**, 219–232.
62 J. H. Park, J. M. Hong, Y. M. Ju, J. W. Jung, H.-W. Kang, S. J. Lee, J. J. Yoo, S. W. Kim, S. H. Kim and D.-W. Cho, *Biomaterials*, 2015, **62**, 106–115.
63 H. Tsukada, S. Gangadharan, R. Garland, F. Herth, M. DeCamp and A. Ernst, *Ann. Thorac. Surg.*, 2010, **90**, 1793–1797.
64 D. H. Reneker and I. Chun, *Nanotechnology*, 1996, **7**, 216–223.
65 E. Biazar and S. H. Keshel, *Cell Commun. Adhes.*, 2013, **20**, 41–49.
66 E. Biazar, M. Ahmadian, S. H. K, A. Gazmeh, S.-F. Mohammadi, A. Lashay, M. Heidari, H. Eslami,

M. Sahebalzamani and H. Hashemi, *Fibers Polym.*, 2017, **18**, 1545–1553.
67 E. Biazar, A. Baradaran-Rafii, S. Heidari-keshel and S. Tavakolifard, *J. Biomater. Sci., Polym. Ed.*, 2015, **26**, 1139–1151.
68 A. Baradaran-Rafii, E. Biazar and S. Heidari-Keshel, *Int. J. Polym. Mater. Polym. Biomater.*, 2015, **64**, 879–887.
69 C. Mahoney, D. Conklin, J. Waterman, J. Sankar and N. Bhattarai, *J. Biomater. Sci., Polym. Ed.*, 2016, **27**, 611–625.
70 C.-H. Lin, J.-M. Su and S.-H. Hsu, *Tissue Eng., Part C*, 2008, **14**, 69–77.
71 F. Baino, G. Novajra and C. Vitale-Brovarone, *Front. Bioeng. Biotechnol.*, 2015, **3**, 202.
72 S. Kargozar, R. K. Singh, H.-W. Kim and F. Baino, *Acta Biomater.*, 2020, **115**, 1–28.
73 P. Saravanapavan, S. Verrier and L. Hench, *Key Eng. Mater.*, 2004, **254–256**, 781–784.
74 W. Lai, P. Ducheyne, J. Garino and C. M. Flaitz, *MRS Online Proc. Libr.*, 1999, **599**, 261.
75 S. Kargozar, S. Hamzehlou and F. Baino, *Materials*, 2017, **10**, 1429.
76 Z. Zhou, L. Xiang, B. Ou, T. Huang, H. Zhou, W. Zeng, L. Liu, Q. Liu, Y. Zhao, S. He and H. Huang, *J. Macromol. Sci., Part A: Pure Appl.Chem.*, 2014, **51**, 572–576.
77 A. Tan, H. Romanska, S. Lenza, J. Jones, L. Hench, J. Polak and A. Bishop, *Key Eng. Mater.*, 2003, **240–242**, 719–724.
78 S. Verrier, J. J. Blaker, V. Maquet, L. L. Hench and A. R. Boccaccini, *Biomaterials*, 2004, **25**, 3013–3021.
79 J. Alijotas-Reig, E. Esteve-Valverde, C. Belizna, A. Selva-O'Callaghan, J. Pardos-Gea, A. Quintana, A. Mekinian, A. Anunciacion-Llunell and F. Miró-Mur, *Autoimmun. Rev.*, 2020, **19**, 102569.
80 J. L. Dziki, L. Huleihel, M. E. Scarritt and S. F. Badylak, *Tissue Eng., Part A*, 2017, **23**, 1152–1159.
81 A. J. Allman, T. B. McPherson, S. F. Badylak, L. C. Merrill, B. Kallakury, C. Sheehan, R. H. Raeder and D. W. Metzger, *Transplantation*, 2001, **71**, 1631–1640.
82 J. E. Valentin, A. M. Stewart-Akers, T. W. Gilbert and S. F. Badylak, *Tissue Eng., Part A*, 2009, **15**, 1687–1694.
83 B. M. Sicari, J. L. Dziki, B. F. Siu, C. J. Medberry, C. L. Dearth and S. F. Badylak, *Biomaterials*, 2014, **35**, 8605–8612.
84 P. F. Slivka, C. L. Dearth, T. J. Keane, F. W. Meng, C. J. Medberry, R. T. Riggio, J. E. Reing and S. F. Badylak, *Biomater. Sci.*, 2014, **2**, 1521–1534.
85 D. M. Faulk, R. Londono, M. T. Wolf, C. A. Ranallo, C. A. Carruthers, J. D. Wildemann, C. L. Dearth and S. F. Badylak, *Biomaterials*, 2014, **35**, 8585–8595.
86 C.-C. Lin, A. T. Metters and K. S. Anseth, *Biomaterials*, 2009, **30**, 4907–4914.
87 S. F. Badylak, *Semin. Cell Dev. Biol.*, 2002, **13**, 377–383.
88 Y. Zhou, J. C. Horowitz, A. Naba, N. Ambalavanan, K. Atabai, J. Balestrini, P. B. Bitterman, R. A. Corley, B.-S. Ding, A. J. Engler, K. C. Hansen, J. S. Hagood, F. Kheradmand, Q. S. Lin, E. Neptune, L. Niklason, L. A. Ortiz, W. C. Parks, D. J. Tschumperlin, E. S. White, H. A. Chapman and V. J. Thannickal, *Matrix Biol.*, 2018, **73**, 77–104.
89 J. E. Nichols, J. A. Niles and J. Cortiella, *Organogenesis*, 2009, **5**, 57–61.
90 M. J. Mondrinos, S. Koutzaki, E. Jiwanmall, M. Li, J.-P. Dechadarevian, P. I. Lelkes and C. M. Finck, *Tissue Eng.*, 2006, **12**, 717–728.
91 M. J. Mondrinos, S. H. Koutzaki, H. M. Poblete, M. C. Crisanti, P. I. Lelkes and C. M. Finck, *Tissue Eng., Part A*, 2008, **14**, 361–368.
92 K. M. Brouwer, H. R. Hoogenkamp, W. F. Daamen and T. H. van Kuppevelt, *Am. J. Respir. Crit. Care Med.*, 2013, **187**, 468–475.
93 A. J. Engler, S. Sen, H. L. Sweeney and D. E. Discher, *Cell*, 2006, **126**, 677–689.
94 C. Coraux, B. Nawrocki-Raby, J. Hinnrasky, C. Kileztky, D. Gaillard, C. Dani and E. Puchelle, *Am. J. Respir. Cell Mol. Biol.*, 2005, **32**, 87–92.
95 T. Li, J. Chang, Y. Zhu and C. Wu, *Adv. Healthcare Mater.*, 2020, **9**, 2000208.
96 B. Grigoryan, S. J. Paulsen, D. C. Corbett, D. W. Sazer, C. L. Fortin, A. J. Zaita, P. T. Greenfield, N. J. Calafat, J. P. Gounley, A. H. Ta, F. Johansson, A. Randles, J. E. Rosenkrantz, J. D. Louis-Rosenberg, P. A. Galie, K. R. Stevens and J. S. Miller, *Science*, 2019, **364**, 458–464.
97 J. He, X. Zhang, X. Xia, M. Han, F. Li, C. Li, Y. Li and D. Gao, *J. Mol. Cell Biol.*, 2020, **12**, 569–579.
98 C. E. Barkauskas, M.-I. Chung, B. Fioret, X. Gao, H. Katsura and B. L. M. Hogan, *Development*, 2017, **144**, 986–997.
99 J. L. McQualter, K. Yuen, B. Williams and I. Bertoncello, *Proc. Natl. Acad. Sci. U. S. A.*, 2010, **107**, 1414–1419.
100 B. R. Dye, P. H. Dedhia, A. J. Miller, M. S. Nagy, E. S. White, L. D. Shea and J. R. Spence, *eLife*, 2016, **5**, e19732.
101 W. J. Zacharias, D. B. Frank, J. A. Zepp, M. P. Morley, F. A. Alkhaleel, J. Kong, S. Zhou, E. Cantu and E. E. Morrisey, *Nature*, 2018, **555**, 251–255.
102 Q. Tan, K. M. Choi, D. Sicard and D. J. Tschumperlin, *Biomaterials*, 2017, **113**, 118–132.
103 COVID-19, https://www.kidney.org/coronavirus/kidney-disease-covid-19, (accessed September 5, 2020).
104 C. Benedetti, M. Waldman, G. Zaza, L. V. Riella and P. Cravedi, *Front. Med.*, 2020, **7**, 423.
105 V. Moulisová, C. Gonzalez-García, M. Cantini, A. Rodrigo-Navarro, J. Weaver, M. Costell, R. Sabater i Serra, M. J. Dalby, A. J. García and M. Salmerón-Sánchez, *Biomaterials*, 2017, **126**, 61–74.
106 A. J. Milici, M. B. Furie and W. W. Carley, *Proc. Natl. Acad. Sci. U. S. A.*, 1985, **82**, 6181–6185.
107 K. H. Moon, I. K. Ko, J. J. Yoo and A. Atala, *Methods*, 2016, **99**, 112–119.
108 A. Raya-Rivera, D. R. Esquiliano, J. J. Yoo, E. Lopez-Bayghen, S. Soker and A. Atala, *Lancet*, 2011, **377**, 1175–1182.

109 X. Jiang, Q. Xiong, G. Xu, H. Lin, X. Fang, D. Cui, M. Xu, F. Chen and H. Geng, *Ann. Biomed. Eng.*, 2015, **43**, 2577–2586.
110 W. Chen, C. Shi, S. Yi, B. Chen, W. Zhang, Z. Fang, Z. Wei, S. Jiang, X. Sun, X. Hou, Z. Xiao, G. Ye and J. Dai, *J. Urol.*, 2010, **183**, 2432–2439.
111 Q. Zou and Q. Fu, *Asian J. Urol.*, 2018, **5**, 57–68.
112 W.-D. Zhu, Y.-M. Xu, C. Feng, Q. Fu and L.-J. Song, *Der Urologe. Ausg. A*, 2011, **50**(11), 1420–1425.
113 Y. Zhao, Y. He, J. Guo, J. Wu, Z. Zhou, M. Zhang, W. Li, J. Zhou, D. Xiao, Z. Wang, K. Sun, Y. Zhu and M. Lu, *Acta Biomater.*, 2015, **23**, 91–102.
114 E. Lih, K. W. Park, S. Y. Chun, H. Kim, T. G. Kwon, Y. K. Joung and D. K. Han, *ACS Appl. Mater. Interfaces*, 2016, **8**, 21145–21154.
115 G. Feng, J. Zhang, Y. Li, Y. Nie, D. Zhu, R. Wang, J. Liu, J. Gao, N. Liu, N. He, W. Du, H. Tao, Y. Che, Y. Xu, D. Kong, Q. Zhao and Z. Li, *J. Am. Soc. Nephrol.*, 2016, **27**, 2357–2369.
116 H. C. Caldas, I. M. M. Fernandes, R. S. Kawasaki-Oyama, M. A. S. F. Baptista, A. M. G. Plepis, V. A. Martins, T. M. Coimbra, E. M. Goloni-Bertollo, D. M. Braile and M. Abbud-Filho, *Exp. Biol. Med.*, 2011, **236**, 746–754.
117 B. B. Ratliff, T. Ghaly, P. Brudnicki, K. Yasuda, M. Rajdev, M. Bank, J. Mares, A. K. Hatzopoulos and M. S. Goligorsky, *Am. J. Physiol.: Renal Physiol.*, 2010, **301**(4), F802–F812.
118 M. L. McFetridge, M. P. Del Borgo, M.-I. Aguilar and S. D. Ricardo, *Clin. Sci.*, 2018, **132**, 1977–1994.
119 E. Lih, W. Park, K. W. Park, S. Y. Chun, H. Kim, Y. K. Joung, T. G. Kwon, J. A. Hubbell and D. K. Han, *ACS Cent. Sci.*, 2019, **5**, 458–467.
120 M. McManus, E. Boland, S. Sell, W. Bowen, H. Koo, D. Simpson and G. Bowlin, *Biomed. Mater.*, 2007, **2**, 257–262.
121 M. Pokrywczynska, A. Jundzill, J. Adamowicz, T. Kowalczyk, K. Warda, M. Rasmus, L. Buchholz, S. Krzyzanowska, P. Nakielski, T. Chmielewski, M. Bodnar, A. Marszalek, R. Debski, M. Frontczak-Baniewicz, G. Mikułowski, M. Nowacki, T. A. Kowalewski and T. Drewa, *PLoS One*, 2014, **9**, e105295.
122 H. Yu, T. Lin, W. Chen, W. Cao, C. Zhang, T. Wang, M. Ding, S. Zhao, H. Wei, H. Guo and X. Zhao, *Biomaterials*, 2019, **219**, 119368.
123 U. Ferrando, A. Dezan, E. Uberti, F. Cauda and G. Pagliano, *Minerva Urol.*, 1981, **33**, 163–168.
124 J. E. Nuininga, M. J. W. Koens, D. M. Tiemessen, E. Oosterwijk, W. F. Daamen, P. J. Geutjes, T. H. van Kuppevelt and W. F. J. Feitz, *Tissue Eng., Part A*, 2010, **16**, 3319–3328.
125 S. J. Lee, H.-J. Wang, T.-H. Kim, J. S. Choi, G. Kulkarni, J. D. Jackson, A. Atala and J. J. Yoo, *Stem Cells Transl. Med.*, 2018, **7**, 241–250.
126 L. A. Ribeiro-Filho and K.-D. Sievert, *Adv. Drug Delivery Rev.*, 2015, **82–83**, 38–46.
127 F. Chen, J. J. Yoo and A. Atala, *Urology*, 1999, **54**, 407–410.
128 F. Mantovani, A. Trinchieri, B. Mangiarotti, M. Nicola, C. Castelnuovo, S. Confalonieri and E. Pisani, *Arch. Ital. Urol. Androl.*, 2002, **74**, 127–128.
129 F. Mantovani, E. Tondelli, G. Cozzi, D. A. El Rahman, M. G. Spinelli, I. Oliva, E. Finkelberg, M. Talso, D. Varisco, A. Maggioni and F. Rocco, *Urologia*, 2011, **78**, 92–97.
130 L. A. Ribeiro-Filho, A. I. Mitre, A. S. Sarkis, P. E. M. Guimaraes, M. A. Arap, I. A. Silva, H. Shiina, M. Igawa, J. W. McAninch, R. Dahiya, E. A. Tanagho and M. Srougi, *J. Urol.*, 2006, **175**, 161–161.
131 L. Ribeiro-Filho, A. Fazoli, M. A. Arap, A. Mitre, R. Falci, J. L. Chambo, A. M. Lucon, H. Shiina, M. Igawa, R. Dahiya, E. Tanagho, W. Nahas and M. Srougi, *J. Urol.*, 2014, **191**, e20.
132 R. Fiala, A. Vidlar, R. Vrtal, K. Belej and V. Student, *Eur. Urol.*, 2007, **51**, 1702–1708.
133 A. El Kassaby, T. AbouShwareb and A. Atala, *J. Urol.*, 2008, **179**, 1432–1436.
134 D. Jothimani, R. Venugopal, M. F. Abedin, I. Kaliamoorthy and M. Rela, *J. Hepatol.*, 2020, **73**, 1231–1240.
135 Z. Fan, L. Chen, J. Li, X. Cheng, J. Yang, C. Tian, Y. Zhang, S. Huang, Z. Liu and J. Cheng, *Clin. Gastroenterol. Hepatol.*, 2020, **18**, 1561–1566.
136 M. V. Lenti, F. Borrelli de Andreis, I. Pellegrino, C. Klersy, S. Merli, E. Miceli, N. Aronico, C. Mengoli, M. Di Stefano, S. Cococcia, G. Santacroce, S. Soriano, F. Melazzini, M. Delliponti, F. Baldanti, A. Triarico, G. R. Corazza, M. Pinzani and A. Di Sabatino, *Intern. Emerg. Med.*, 2020, **15**, 1399–1407.
137 P. Matar, L. Alaniz, V. Rozados, J. B. Aquino, M. Malvicini, C. Atorrasagasti, M. Gidekel, M. Silva, O. G. Scharovsky and G. Mazzolini, *J. Biomed. Sci.*, 2009, **16**, 30.
138 C. Zhang, L. Shi and F.-S. Wang, *Lancet Gastroenterol. Hepatol.*, 2020, **5**, 428–430.
139 X. Chai, L. Hu, Y. Zhang, W. Han, Z. Lu, A. Ke, J. Zhou, G. Shi, N. Fang, J. Fan, J. Cai, J. Fan and F. Lan, *bioRxiv*, 2020, DOI: 10.1101/2020.02.03.931766.
140 T. T. Sahin, S. Akbulut and S. Yilmaz, *World J. Gastroenterol.*, 2020, **26**, 2987–2999.
141 G. Mazza, W. Al-Akkad, K. Rombouts and M. Pinzani, *Hepatol. Commun.*, 2018, **2**, 131–141.
142 R. A. Perez, C.-R. Jung and H.-W. Kim, *Adv. Healthcare Mater.*, 2017, **6**, 1600791.
143 J.-X. Xiang, X.-L. Zheng, R. Gao, W.-Q. Wu, X.-L. Zhu, J.-H. Li and Y. Lv, *Hepatobiliary Pancreatic Dis. Int.*, 2015, **14**, 502–508.
144 A. da Silva Morais, S. Vieira, X. Zhao, Z. Mao, C. Gao, J. M. Oliveira and R. L. Reis, *Adv. Healthcare Mater.*, 2020, **9**, 1901435.
145 B. E. Uygun, A. Soto-Gutierrez, H. Yagi, M.-L. Izamis, M. A. Guzzardi, C. Shulman, J. Milwid, N. Kobayashi, A. Tilles, F. Berthiaume, M. Hertl, Y. Nahmias, M. L. Yarmush and K. Uygun, *Nat. Med.*, 2010, **16**, 814–820.
146 G. Mazza, K. Rombouts, A. Rennie Hall, L. Urbani, T. Vinh Luong, W. Al-Akkad, L. Longato, D. Brown,

P. Maghsoudlou, A. P. Dhillon, B. Fuller, B. Davidson, K. Moore, D. Dhar, P. De Coppi, M. Malago and M. Pinzani, *Sci. Rep.*, 2015, **5**, 13079.
147 P. M. Baptista, M. M. Siddiqui, G. Lozier, S. R. Rodriguez, A. Atala and S. Soker, *Hepatology*, 2011, **53**, 604–617.
148 M. K. Saums, W. Wang, B. Han, L. Madhavan, L. Han, D. Lee and R. G. Wells, *Langmuir*, 2014, **30**, 5481–5487.
149 A. P. Kourouklis, K. B. Kaylan and G. H. Underhill, *Biomaterials*, 2016, **99**, 82–94.
150 L. K. Kanninen, P. Porola, J. Niklander, M. M. Malinen, A. Corlu, C. Guguen-Guillouzo, A. Urtti, M. L. Yliperttula and Y.-R. Lou, *Exp. Cell Res.*, 2016, **341**, 207–217.
151 S. Ogiso, K. Yasuchika, K. Fukumitsu, T. Ishii, H. Kojima, Y. Miyauchi, R. Yamaoka, J. Komori, H. Katayama, T. Kawai, E. Y. Yoshitoshi, S. Kita, K. Yasuda and S. Uemoto, *Sci. Rep.*, 2016, **6**, 35887.
152 F. T. Lee-Montiel, S. M. George, A. H. Gough, A. D. Sharma, J. Wu, R. DeBiasio, L. A. Vernetti and D. L. Taylor, *Exp. Biol. Med.*, 2017, **242**, 1617–1632.
153 L. A. Vernetti, N. Senutovitch, R. Boltz, R. DeBiasio, T. Ying Shun, A. Gough and D. L. Taylor, *Exp. Biol. Med.*, 2016, **241**, 101–114.
154 D. Vyas, P. M. Baptista, M. Brovold, E. Moran, M. Brovold, B. Gaston, C. Booth, M. Samuel, A. Atala and S. Soker, *Hepatology*, 2018, **67**, 750–761.
155 S. W. Lee, D. J. Jung and G. S. Jeong, *Tissue Eng. Regener. Med.*, 2020, **17**, 731–745.
156 L. Broutier, A. Andersson-Rolf, C. J. Hindley, S. F. Boj, H. Clevers, B.-K. Koo and M. Huch, *Nat. Protoc.*, 2016, **11**, 1724–1743.
157 T. Agarwal, B. Subramanian and T. K. Maiti, *ACS Biomater. Sci. Eng.*, 2019, **5**, 4167–4182.
158 E. Jain, A. Damania and A. Kumar, *Hepatol. Int.*, 2014, **8**, 185–197.
159 M. Bhattacharya, M. M. Malinen, P. Lauren, Y.-R. Lou, S. W. Kuisma, L. Kanninen, M. Lille, A. Corlu, C. GuGuen-Guillouzo, O. Ikkala, A. Laukkanen, A. Urtti and M. Yliperttula, *J. Controlled Release*, 2012, **164**, 291–298.
160 M. Dvir-Ginzberg, I. Gamlieli-Bonshtein, R. Agbaria and S. Cohen, *Tissue Eng.*, 2003, **9**, 757–766.
161 E. Shteyer, A. B. Ya'acov, L. Zolotaryova, A. Sinai, Y. Lichtenstein, O. Pappo, O. Kryukov, T. Elkayam, S. Cohen and Y. Ilan, *Acta Biomater.*, 2014, **10**, 3209–3216.
162 S.-J. Seo, I.-Y. Kim, Y.-J. Choi, T. Akaike and C.-S. Cho, *Biomaterials*, 2006, **27**, 1487–1495.
163 A. S. Hayward, A. M. Eissa, D. J. Maltman, N. Sano, S. A. Przyborski and N. R. Cameron, *Biomacromolecules*, 2013, **14**, 4271–4277.
164 E. Török, M. Lutgehetmann, J. Bierwolf, S. Melbeck, J. Düllmann, B. Nashan, P. X. Ma and J. M. Pollok, *Liver Transpl.*, 2011, **17**, 104–114.
165 J. Kasuya, R. Sudo, R. Tamogami, G. Masuda, T. Mitaka, M. Ikeda and K. Tanishita, *Biomaterials*, 2012, **33**, 2693–2700.
166 Y. Qiu, Z. Mao, Y. Zhao, J. Zhang, Q. Guo, Z. Gou and C. Gao, *Macromol. Res.*, 2012, **20**, 283–291.
167 V. L. Tsang, A. A. Chen, L. M. Cho, K. D. Jadin, R. L. Sah, S. DeLong, J. L. West and S. N. Bhatia, *FASEB J.*, 2007, **21**, 790–801.
168 M. Ghibaudo, L. Trichet, J. Le Digabel, A. Richert, P. Hersen and B. Ladoux, *Biophys. J.*, 2009, **97**, 357–368.
169 A. Ananthanarayanan, B. C. Narmada, X. Mo, M. McMillian and H. Yu, *Trends Biotechnol.*, 2011, **29**, 110–118.
170 E. S. Carlisle, M. R. Mariappan, K. D. Nelson, B. E. Thomes, R. B. Timmons, A. Constantinescu, R. C. Eberhart and P. E. Bankey, *Tissue Eng.*, 2000, **6**, 45–52.
171 H.-J. Lee, M. J. Son, J. Ahn, S. J. Oh, M. Lee, A. Kim, Y.-J. Jeung, H.-G. Kim, M. Won, J. H. Lim, N.-S. Kim, C.-R. Jung and K.-S. Chung, *Acta Biomater.*, 2017, **64**, 67–79.
172 Y. Du, R. Han, F. Wen, S. Ng San San, L. Xia, T. Wohland, H. L. Leo and H. Yu, *Biomaterials*, 2008, **29**, 290–301.
173 J. H. Hong, H. J. Lee and B. Jeong, *ACS Appl. Mater. Interfaces*, 2017, **9**, 11568–11576.
174 H. Wood, *Nat. Rev. Neurol.*, 2020, **16**, 403–403.
175 D. Nuzzo and P. Picone, *Neurosci. Res.*, 2020, **158**, 1–5.
176 How COVID-19 Affects the Brain in Neuroimaging, https://www.itnonline.com/article/how-covid-19-affects-brain-neuroimaging, (accessed September 6, 2020).
177 M. Sheraton, N. Deo, R. Kashyap and S. Surani, *Cureus.*, 2020, **12**, e8192.
178 D. Orsucci, E. C. Ienco, G. Nocita, A. Napolitano and M. Vista, *Drugs Context.*, 2020, **9**, 2020.
179 M. A. Ellul, L. Benjamin, B. Singh, S. Lant, B. D. Michael, A. Easton, R. Kneen, S. Defres, J. Sejvar and T. Solomon, *Lancet Neurol.*, 2020, **19**, 767–783.
180 J. Helms, S. Kremer, H. Merdji, R. Clere-Jehl, M. Schenck, C. Kummerlen, O. Collange, C. Boulay, S. Fafi-Kremer, M. Ohana, M. Anheim and F. Meziani, *N. Engl. J. Med.*, 2020, **382**, 2268–2270.
181 M. Francesca, B. Lia and C. Antonio, *Med. Case Rep.*, 2020, **6**, 143.
182 M. D. Neher, S. Weckbach, M. A. Flierl, M. S. Huber-Lang and P. F. Stahel, *J. Biomed. Sci.*, 2011, **18**, 90.
183 J. T. S. Pettikiriarachchi, C. L. Parish, M. S. Shoichet, J. S. Forsythe and D. R. Nisbet, *Aust. J. Chem.*, 2010, **63**, 1143–1154.
184 A. Subramanian, U. M. Krishnan and S. Sethuraman, *J. Biomed. Sci.*, 2009, **16**, 108.
185 T. Führmann, P. N. Anandakumaran and M. S. Shoichet, *Adv. Healthcare Mater.*, 2017, **6**, 1601130.
186 S. H. Bhang, S. Lee, J.-Y. Shin, T.-J. Lee and B.-S. Kim, *Tissue Eng., Part A*, 2012, **18**, 2138–2147.
187 R. M. Namba, A. A. Cole, K. B. Bjugstad and M. J. Mahoney, *Acta Biomater.*, 2009, **5**, 1884–1897.
188 Y.-T. Wei, X.-D. Sun, X. Xia, F.-Z. Cui, Y. He, B.-F. Liu and Q.-Y. Xu, *J. Bioact. Compat. Polym.*, 2009, **24**, 205–219.
189 Y.-J. Ren, Z.-Y. Zhou, F.-Z. Cui, Y. Wang, J.-P. Zhao and Q.-Y. Xu, *J. Bioact. Compat. Polym.*, 2009, **24**, 56–62.

190 S. H. Bhang, T.-J. Lee, J. M. Lim, J. S. Lim, A. M. Han, C. Y. Choi, Y. H. Kim Kwon and B.-S. Kim, *Biomaterials*, 2009, **30**, 126–132.
191 T. Xu, P. Molnar, C. Gregory, M. Das, T. Boland and J. J. Hickman, *Biomaterials*, 2009, **30**, 4377–4383.
192 L. Pan, Y. Ren, F. Cui and Q. Xu, *J. Neurosci. Res.*, 2009, **87**, 3207–3220.
193 F. Z. Cui, W. M. Tian, S. P. Hou, Q. Y. Xu and I.-S. Lee, *J. Mater. Sci. Mater. Med.*, 2006, **17**, 1393–1401.
194 S. Hou, Q. Xu, W. Tian, F. Cui, Q. Cai, J. Ma and I.-S. Lee, *J. Neurosci. Methods*, 2005, **148**, 60–70.
195 H. Xu, L. Zhang, Y. Bao, X. Yan, Y. Yin, Y. Li, X. Wang, Z. Huang and P. Xu, *J. Bioact. Compat. Polym.*, 2017, **32**, 146–162.
196 H. Itosaka, S. Kuroda, H. Shichinohe, H. Yasuda, S. Yano, S. Kamei, R. Kawamura, K. Hida and Y. Iwasaki, *Neuropathology*, 2009, **29**, 248–257.
197 P. J. Johnson, S. R. Parker and S. E. Sakiyama-Elbert, *J. Biomed. Mater. Res., Part A*, 2010, **92**, 152–163.
198 A. Samadikuchaksaraei, *J Neuroeng Rehabil*, 2007, **4**, 15.
199 H. R. Irons, D. K. Cullen, N. P. Shapiro, N. A. Lambert, R. H. Lee and M. C. LaPlaca, *J. Neural Eng.*, 2008, **5**, 333–341.
200 P. Lesný, J. De Croos, M. Přádný, J. Vacík, J. Michálek, S. Woerly and E. Syková, *J. Chem. Neuroanat.*, 2002, **23**, 243–247.
201 S. Woerly, S. Fort, I. Pignot-Paintrand, C. Cottet, C. Carcenac and M. Savasta, *Biomacromolecules*, 2008, **9**, 2329–2337.
202 Y. Zhong and R. V. Bellamkonda, *J. R. Soc., Interface*, 2008, **5**, 957–975.
203 S. R. Hynes, L. M. McGregor, M. F. Rauch and E. B. Lavik, *J. Biomater. Sci., Polym. Ed.*, 2007, **18**, 1017–1030.
204 P. D. Dalton, L. Flynn and M. S. Shoichet, *Biomaterials*, 2002, **23**, 3843–3851.
205 J. Xie, M. R. MacEwan, S. M. Willerth, X. Li, D. W. Moran, S. E. Sakiyama-Elbert and Y. Xia, *Adv. Funct. Mater.*, 2009, **19**, 2312–2318.
206 J. Y. Lee, C. A. Bashur, A. S. Goldstein and C. E. Schmidt, *Biomaterials*, 2009, **30**, 4325–4335.
207 M. A. Lancaster, N. S. Corsini, S. Wolfinger, E. H. Gustafson, A. W. Phillips, T. R. Burkard, T. Otani, F. J. Livesey and J. A. Knoblich, *Nat. Biotechnol.*, 2017, **35**, 659–666.
208 A. A. Mansour, J. T. Gonçalves, C. W. Bloyd, H. Li, S. Fernandes, D. Quang, S. Johnston, S. L. Parylak, X. Jin and F. H. Gage, *Nat. Biotechnol.*, 2018, **36**, 432–441.
209 J. H. Collier, *Soft Matter*, 2008, **4**, 2310–2315.
210 G. A. Silva, *Surg. Neurol.*, 2005, **63**, 301–306.
211 G. A. Silva, C. Czeisler, K. L. Niece, E. Beniash, D. A. Harrington, J. A. Kessler and S. I. Stupp, *Science*, 2004, **303**, 1352–1355.
212 T. C. Holmes, S. de Lacalle, X. Su, G. Liu, A. Rich and S. Zhang, *Proc. Natl. Acad. Sci. U. S. A.*, 2000, **97**, 6728–6733.
213 J. Guo, K. K. G. Leung, H. Su, Q. Yuan, L. Wang, T.-H. Chu, W. Zhang, J. K. S. Pu, G. K. P. Ng, W. M. Wong, X. Dai and W. Wu, *Nanomedicine*, 2009, **5**, 345–351.
214 R. Boni, A. Ali, A. Shavandi and A. N. Clarkson, *J. Biomed. Sci.*, 2018, **25**, 90.
215 S. J. Archibald, J. Shefner, C. Krarup and R. D. Madison, *J. Neurosci.*, 1995, **15**, 4109–4123.
216 S. E. Mackinnon and A. L. Dellon, *J. Reconstr. Microsurg.*, 1990, **6**, 117–121.
217 F. Gonzalez-Perez, S. Cobianchi, C. Heimann, J. B. Phillips, E. Udina and X. Navarro, *Neurosurgery*, 2017, **80**, 465–474.
218 K. J. Wangensteen and L. K. Kalliainen, *Hand*, 2010, **5**, 273–277.
219 A. Bozkurt, K. G. Claeys, S. Schrading, J. V. Rödler, H. Altinova, J. B. Schulz, J. Weis, N. Pallua and S. G. A. van Neerven, *Eur. J. Med. Res.*, 2017, **22**, 34.
220 V. Benfenati, K. Stahl, C. Gomis-Perez, S. Toffanin, A. Sagnella, R. Torp, D. L. Kaplan, G. Ruani, F. G. Omenetto, R. Zamboni and M. Muccini, *Adv. Funct. Mater.*, 2012, **22**, 1871–1884.
221 C. G. Gennari, F. Cilurzo, N. Mitro, D. Caruso, P. Minghetti and V. Magnaghi, *Regener. Med.*, 2017, **13**, 141–157.
222 K. E. Crompton, J. D. Goud, R. V. Bellamkonda, T. R. Gengenbach, D. I. Finkelstein, M. K. Horne and J. S. Forsythe, *Biomaterials*, 2007, **28**, 441–449.
223 C. M. Valmikinathan, V. J. Mukhatyar, A. Jain, L. Karumbaiah, M. Dasari and R. V. Bellamkonda, *Soft Matter*, 2012, **8**, 1964–1976.
224 M. S. Kim, J. W. Kim and J. K. Hyun, *J. Neurol. Sci.*, 2017, **381**, 612–613.
225 S. Farzamfar, F. Esmailpour, M. Rahmati, A. Vaez, M. Mirzaii, B. Garmabi, A. Shayannia, E. Ebrahimi, H. Vahedi and M. Salehi, *Int. J. Health Stud.*, 2017, DOI: 10.22100/ijhs.v3i2.236.
226 M. J. Mahoney and K. S. Anseth, *Biomaterials*, 2006, **27**, 2265–2274.
227 U. Freudenberg, A. Hermann, P. B. Welzel, K. Stirl, S. C. Schwarz, M. Grimmer, A. Zieris, W. Panyanuwat, S. Zschoche, D. Meinhold, A. Storch and C. Werner, *Biomaterials*, 2009, **30**, 5049–5060.
228 L. Ghasemi-Mobarakeh, M. P. Prabhakaran, M. Morshed, M.-H. Nasr-Esfahani and S. Ramakrishna, *Biomaterials*, 2008, **29**, 4532–4539.
229 D. Gupta, J. Venugopal, M. P. Prabhakaran, V. R. G. Dev, S. Low, A. T. Choon and S. Ramakrishna, *Acta Biomater.*, 2009, **5**, 2560–2569.
230 M. A. Alvarez-Perez, V. Guarino, V. Cirillo and L. Ambrosio, *Biomacromolecules*, 2010, **11**, 2238–2246.
231 A. Kriebel, D. Hodde, T. Kuenzel, J. Engels, G. Brook and J. Mey, *J. Tissue Eng. Regener. Med.*, 2017, **11**, 3289–3304.
232 A. Cooper, N. Bhattarai and M. Zhang, *Carbohydr. Polym.*, 2011, **85**, 149–156.
233 Y.-C. Kuo, C.-F. Yeh and J.-T. Yang, *Biomaterials*, 2009, **30**, 6604–6613.

234 C. Xue, N. Hu, Y. Gu, Y. Yang, Y. Liu, J. Liu, F. Ding and X. Gu, *Neurorehabil. Neural Repair*, 2012, **26**, 96–106.
235 C. Liu, Y. Huang, M. Pang, Y. Yang, S. Li, L. Liu, T. Shu, W. Zhou, X. Wang, L. Rong and B. Liu, *PLoS One*, 2015, **10**, e0117709.
236 Y.-C. Yang, C. C. Shen, H.-C. Cheng and L. Bai, *J. Biomed. Mater. Res., Part A*, 2011, **96**, 288–300.
237 F. Faghihi, E. Mirzaei, J. Ai, A. Lotfi, F. A. Sayahpour, S. E. Barough and M. T. Joghataei, *Mol. Neurobiol.*, 2016, **53**, 1862–1872.
238 L. Tian, M. P. Prabhakaran, J. Hu, M. Chen, F. Besenbacher and S. Ramakrishna, *RSC Adv.*, 2015, **5**, 49838–49848.
239 T. M. Dinis, R. Elia, G. Vidal, Q. Dermigny, C. Denoeud, D. L. Kaplan, C. Egles and F. Marin, *J. Mech. Behav. Biomed. Mater.*, 2015, **41**, 43–55.
240 C. Xue, H. Zhu, D. Tan, H. Ren, X. Gu, Y. Zhao, P. Zhang, Z. Sun, Y. Yang, J. Gu, Y. Gu and X. Gu, *J. Tissue Eng. Regener. Med.*, 2018, **12**, e1143–e1153.
241 Z. Zhang, M. Rouabhia, Z. Wang, C. Roberge, G. Shi, P. Roche, J. Li and L. H. Dao, *Artif. Organs*, 2007, **31**, 13–22.
242 Z. Shi, H. Gao, J. Feng, B. Ding, X. Cao, S. Kuga, Y. Wang, L. Zhang and J. Cai, *Angew. Chem.*, 2014, **126**, 5484–5488.
243 B. Guo and P. X. Ma, *Biomacromolecules*, 2018, **19**, 1764–1782.
244 J. H. Collier, J. P. Camp, T. W. Hudson and C. E. Schmidt, *J. Biomed. Mater. Res.*, 2000, **50**, 574–584.
245 S.-Z. Yow, T. H. Lim, E. K. F. Yim, C. T. Lim and K. W. Leong, *Polymers*, 2011, **3**, 527–544.
246 S. Wang, C. Sun, S. Guan, W. Li, J. Xu, D. Ge, M. Zhuang, T. Liu and X. Ma, *J. Mater. Chem. B*, 2017, **5**, 4774–4788.