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Fibrosis in tissue engineering and regenerative medicine: treat or trigger?

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ABSTRACT

Fibrosis is a life-threatening pathological condition resulting from a dysfunctional tissue repair process. There is no efficient treatment and organ transplantation is in many cases the only therapeutic option.
Here we review tissue engineering and regenerative medicine (TERM) approaches to address fibrosis in the cardiovascular system, the kidney, the lung and the liver. These strategies have great potential to achieve repair or replacement of diseased organs by cell- and material-based therapies. However, paradoxically, they might also trigger fibrosis. Cases of TERM interventions with adverse outcome are also included in this review. Furthermore, we emphasize the fact that, although organ engineering is still in its infancy, the advances in the field are leading to biomedically relevant *in vitro* models with tremendous potential for disease recapitulation and development of therapies. These human tissue models might have increased predictive power for human drug responses thereby reducing the need for animal testing.

Contents

Abbreviations: ECM, extracellular matrix; TE, tissue engineering; TERM, tissue engineering and regenerative medicine; MMPs, matrix metalloproteinases; iPSCs, induced pluripotent stem cells; HVTE, heart valve tissue engineering; TEHV, tissue-engineered heart valve; EMT, epithelial-to-mesenchymal transition; VIC, valvular interstitial cell; EPC, endothelial progenitor cell; MSC, mesenchymal stem cell; iMSC, induced mesenchymal stem cell; ADSC, adipose derived stem cell; IPF, idiopathic pulmonary fibrosis; AEC2, type 2 alveolar epithelial cell; BM, bone marrow; HCC, hepatocellular carcinoma.

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1. Introduction

Tissue damage can be caused by a variety of acute or chronic stimuli, including environmental and pharmacological insults, infections, autoimmune reactions, surgery, and mechanical injury. The repair process is a complex cascade of molecular and cellular events, which results in the replacement of damaged or dead cells, as well as the remodelling of the extracellular matrix (ECM) to restore the normal parenchymal tissue. The acute wound healing response can be broken down into hemostasis, inflammation, activation and proliferation of collagen-producing cells, tissue remodelling and resolution. This process is of fundamental importance for survival; however, it might become pathological if the resolution phase is not completed. In this case, the remodelling progresses into an exaggerated and uncontrolled deposition of ECM. This results in the formation of a permanent scar tissue during a chronic inflammatory reaction, in which inflammation, tissue destruction, and repair processes occur simultaneously [1,2]. Fibrotic lesions might affect major organs, including the lungs, the kidneys, the cardiovascular system and the liver. The excessive accumulation of ECM progressively alters the normal tissue architecture compromising the function and eventually leading to organ failure and death.

It is estimated that fibroproliferative diseases directly or indirectly account for almost 45% of deaths in the developed world [3], representing a major health and socio-economic burden. No efficient therapies are available to halt and reverse fibrosis, and organ transplantation is the only curative option for many fibrotic conditions. Donor organ shortage and all the complications associated with transplantation make the development of new therapies imperative.

In this review, we explore the potential of tissue engineering and regenerative medicine (TERM) approaches to treat fibrosis. Bioengineered organs could be a replacement option to overcome the donor shortage. Despite being still in its infancy, the *de novo* creation of functional complex whole organs is showing promising preclinical outcomes. On the other side, cell delivery to the fibrotic tissues has already been implemented in the clinical settings in order to inhibit disease progression and restore organ's functionality. However, concerns have arisen that these therapies themselves can trigger host repair mechanisms resulting in fibrotic reactions.

In this sense, we will critically review the current state of TERM strategies to address fibrosis in the cardiovascular system, the kidney, the lung and the liver, by discussing the proposed solutions ('treat') and then highlighting the cases in which fibrosis developed as an unwanted result of the regenerative treatment ('trigger'). Furthermore, we will address the tremendous potential of bioengineered human tissues as *in vitro* models to i) investigate molecular and cellular mechanisms in controlled biomimetic environments and ii) to develop and test novel pharmaceutical therapies for the treatment of fibrosis (Fig 1).

1.1. Fibrosis in tissue engineering and regenerative medicine

Tissue engineering (TE) aims at developing healthy autologous tissue equivalents by employing the patient's own cells to replace native diseased tissues. This can be achieved either by engineering a cell-based construct *in vitro* by e.g. conditioning a cell-seeded scaffold in a bioreactor and then implanting it into the recipient (classical TE approach) [4] or by implanting a cell-free matrix able to elicit a foreign body response with subsequent cell infiltration and final resolution of inflammation (*in situ* TE) [5,6]. Depending on the tissue to be engineered (e.g. cardiovascular, respiratory, renal, hepatic, etc.) and the chosen approach, different aspects have to be defined, e.g. the scaffold material, the fabrication technique and the 3D architecture, the cell sources, the mechanical and biochemical *in vitro* stimulation regime. The intended final result, independently of the applied strategy, is an autologous tissue potentially capable of growing and self-repairing. This represents a fascinatedly straightforward concept which, however, requires a thorough understanding of how cells interact with biomaterials, forces and soluble factors to guide cell remodelling towards an healthy tissue, rather than a fibrotic one [7–10].

The danger to be avoided is, indeed, to substitute a native pathological tissue with a disease-prone one [7]. Mechanical and biochemical stimulations are normally used in TE to increase ECM production and, therefore, tissue growth. This happens via the differentiation of the cells populating the scaffold into tissue-synthesizing, contractile myofibroblasts, i.e. the hallmark of tissue repair and fibrogenesis [8]. This process can become unstable resulting in a fibrocontractive remodelling through sustained myofibrogenesis. This might continue *in vivo* and even be exacerbated by the inflammatory response associated with the implantation, a typical host's immune response to any kind of implant [10].

Peri-implantational fibrosis represents a main clinical concern as it results in the impaired function of the implant [8]. Any regenerative approach intended to reestablish tissue functionality, must consider the central role that the immune system plays in tissue repair to avoid a chronic inflammation and hence fibrosis [11]. Macrophages play a critical role at all stages of tissue repair and fibrosis [12,13]. This has prompted the development of new strategies in TERM that aim at modulating the macrophages' activation state in order to guide the host response towards healing rather than chronic inflammation. The physicochemical properties of the implant (i.e. porosity, surface chemistry, surface topography, mechanical properties) have been shown to have an influence on the polarization of the macrophages. Tuning these properties is, therefore, a way to create immunoinstructive constructs, as thoroughly addressed in many recent reviews [14–17]. Loading the scaffold with therapeutic agents (e.g. cytokines, anti-inflammatory peptides, interfering RNAs, aptamers) to be released *in situ* to modulate macrophage polarization is another strategy followed by several research groups [18]. It is clear that a deep understanding of the role of the immune system and the influence of patient-specific factors in tissue repair is mandatory to bring these strategies to success [19]. The ultimate goal is the development of immunoinstructive implants, which should provide a tailored microenvironment for the guided interplay between immune cells, stem/progenitor cells and tissue cells directly at the site of implantation, resulting in functional tissue regeneration [5,6].

Conversely, in cell-therapies, cells are introduced in an already existing microenvironment, that is the diseased tissue/organ. The influence that physicochemical properties have on the cells and specifically on their differentiation has to be taken into account when analysing the outcome of such therapies. Stem cells differentiation towards myofibroblasts participating into the fibrotic process can be induced by the ECM they get in contact with upon delivery/ homing. This directly implicates that the time of delivery with respect to the ECM configuration associated to the fibrosis stage is of crucial importance for the final therapeutic effect [20,21]. Indeed, the ECM plays an active role in

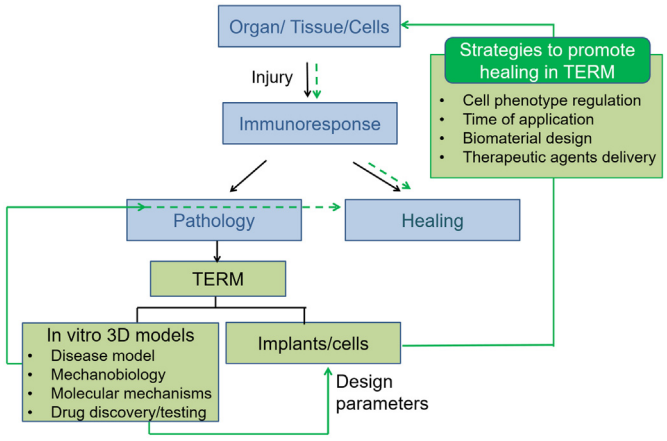


Fig 1. Schematic representation of the role and challenges of TERM in fibrosis. Tissue engineering aims at developing healthy, functional biological equivalents to substitute diseased organs. Delivery of cells to the fibrotic tissues is another approach to inhibit disease progression and restore organ's functionality. However, these interventions, as any other graft, trigger immune and inflammatory responses in an already compromised microenvironment. Strategies have been developed to modulate the immune response towards a healing process and to obtain the integration of a functional organ/tissue. Biomaterial physicochemical properties are critical players in this process. Furthermore, therapeutic agents can be incorporated into the implants in order to promote healing. Equally importantly, implanted/injected cells must acquire the correct tissue-specific phenotype and not participate to the dysregulated repair process. Here the time of delivery with respect to the stage of disease progression might crucially influence the outcome. Tissue-engineered constructs have also the potential to function as biologically relevant 3D in vitro models to study disease onset and progression, as well as to design new therapeutic compounds and to test drugs' efficacy and safety. The models can ultimately provide knowledge to advance and improve implants formulations.

promoting fibrosis progression. The matrix stiffening activates resident and recruited cells that will further contribute to the excessive ECM accumulation in a sort of positive feedback-loop through which fibrosis perpetuates itself [22].

Along the same line of reasoning is the interpretation of *in vitro* results obtained on cell seeding of decellularized organs. Stem cells differentiated into tissue-specific phenotypes or into myofibroblasts when placed in contact with ECMs derived from healthy or diseased subjects, respectively [23]. These findings open a very interesting scenario for *in vitro* models to investigate fibrosis.

The need to develop *in vitro* systems able to recapitulate defined aspects of fibroproliferative processes to study the disease and to enable the formulation and testing of new therapeutic compounds is discussed in the next section.

1.2. Fibrosis models: the need for advanced in vitro models

Animal models are the main tool to investigate initiation and development of fibrosis and to test the effects of anti-fibrotic therapies. Typically, fibrosis is induced in rodent models by administration of substances such as toxins (e.g. carbon tetracloride for liver fibrosis) and chemotherapeutic agents (e.g bleomycin for pulmonary fibrosis), mechanically by ligation of the bile duct or obstruction of the urethra for liver and kidney fibrosis respectively [1], by irradiation or instillation of inorganic particles (e.g. for pulmonary fibrosis), by cytokine injection (TGF-β) and overexpression via gene-transfer, as well as by transgenic approaches [24]. These preclinical models are undoubtedly important as they provide a complete biological environment. In addition, innovative genetic and molecular technologies (e.g. genetic ablation or transgenic overexpression of a specific molecule) provide exciting tools to study signalling pathways involved in a specific disease. However, results from such complex systems might be difficult to interpret and the animal-to-human variability limits their capability to predict human physiological responses in terms of efficacy and toxicity. This explains the high failure rate of new drugs when translated from animal studies to human clinical trials [25–27]. For example, pharmacological compounds targeting the TGF-β pathway or antifibrotic strategies aiming at inhibiting collagen crosslinking were successfully tested in several preclinical studies, but did not show benefits in clinical settings [28–32]. Furthermore, the evaluation endpoints and the methods of assessment of drug efficacy might be different in preclinical and clinical trials [33,34], contributing to the poor predictive values of animal experiments. To overcome the obvious limitations of the animal models in recapitulating the human pathophysiology, attempts have been carried out to create 'humanized' mouse models, or mouse-human chimeras, by engrafting immunodeficient mice with human cells or tissues, or mice that transgenically express human genes [35]. As an example, humanized models have been developed to study lung and liver fibrosis [24,36–38]. Although they have shown great potential for translational biomedical research, some remaining limitations need to be addressed such as the weaker antiviral immune response compared to humans [36]. Additionally, an increasing ethical concern on the use of animal models has stimulated the critical revision of preclinical experiments according to the 3Rs principles [39] and the use of alternative models.

Explanted or biopsied human tissues have also been used as models of fibrosis. However, multiple biopsies from the same patient for research purposes are difficult to obtain because of medical and ethical concerns. Therefore, the information gained from these tissues, albeit of great importance, is typically restricted to a 'snapshot' of an advanced state of the disease [40]. Precision-cut slices of healthy and diseased organs provide the native tissue architecture and contain the complete cell populations. However, their survival is limited to a few days, therefore excluding studies on chronic responses [40–45]. Perfusion of the slices might prolong their longevity in culture but not necessarily their functionality [46,47]. Classical *in vitro* 2D cell culture models and 3D macroscale hydrogel systems offer the possibility to work with human cells and are more controllable than animal models, but can result in oversimplifications with limited significance. For example, *in vitro* ECM degradation studies to investigate the function of individual matrix metalloproteinases (MMPs) in fibrosis have shown high redundancy among the different MMPs, whereas *in vivo* the functions of individual MMPs are specific and unique [1]. In 2D fibrosis models based on the activation of the matrix-synthezising cells in plastic tissue culture dishes, the substrate's stiffness plays an important role. In fact, it induces activation of the freshly isolated quiescent cells. However, the gene expression profiles are different to the ones shown by activated cells in the *in vivo* diseased organs [48,49]. 3D hydrogel-based systems have been developed to provide a more natural environment to the cells. It is very well accepted that cell behaviour in 2D and 3D differs significantly and that composition and architecture of the material, in which cells are cultured, greatly affects it [50,51]. Still, basic 3D systems also suffer from not being capable of reproducing physiological properties, such as the tissue architecture and composition, cell–cell and cell–ECM interactions, as well as the complex mechanobiology of the native tissues.

TE can provide advanced biomimetic *in vitro* models, by exploiting the progress in areas such as stem cell biology, genomics, proteomics, biomaterials development, microfluidics and biofabrication technologies, which was originally driven by the clinical need for bioengineered substitutes.

Besides the general consensus on the need to exactly reproduce the 3D architectures of multicellular systems to generate biomedically relevant models, there is also an increasing awareness of the need to recapitulate the organ-specific mechanical stimuli, as they exert a central effect in the modulation of signalling pathways [31,52–54]. Understanding the molecular mechanisms through which the microenvironment promotes cellular activation will allow to develop therapies that can target the early stages of fibrosis at the transcriptional level and, possibly, even reverse it [55].

To this end, bioreactor technologies have greatly advanced the state of *in vitro* systems by providing controlled dynamic mechanical environment over a wide scale range, from microfluidic platforms to whole-organ bioreactors.

The current state in the development of advanced models to simulate pathologic responses to injury and development of fibrosis in the cardiovascular (section 2.3), renal (section 3.3), pulmonary (section 4.3) and hepatic (section 5.3) tissues will be addressed in this review.

2. Fibrosis in cardiovascular TERM

Cardiovascular fibrosis occurs in the heart and related structures as a pathological consequence of injury. It is mainly mediated by a response to myocardial infarction but it can also affect the heart valve apparatus after genetic, acquired or rheumatic diseases. Precise information on its general prevalence is missing, but its trend is mostly correlated with the onset and progression of specific cardiovascular diseases. For example, 1-2% of patients with heart failure develops also myocardial fibrosis [56].

Heart valve degeneration is a chronic disease with multifactorial nature, but similar pathological development (disorganization of the ECM, tissue fibrosis and leaflet dysfunction). This pathology is generally asymptomatic until its end-stage development and is commonly treated by valve replacement. Increased collagen deposition, along with the accumulation of calcium starting at the fibrous layer, contributes to valvular thickening and rigidity, which leads to valvular stenosis [57,58].

Arterial vessels may be affected by atherosclerotic processes, i.e. fibrofatty deposition and wall stiffening, with serious complications in the late development of the disease, such as ischemic events in the heart and the brain, and locomotor disabilities. Blood vessel stiffening and dysfunction have been reported in cases of pulmonary, hepatic and cystic fibrosis [59–61].

A common hallmark in cardiovascular fibrosis is the activation of cardiac mesenchymal cells, i.e. the fibroblastoid cells of the myocardium, the valvular interstitial cells (VICs) and the smooth muscle cells in the *tunica media*. The mechanical alterations induced by injury are responsible for the molecular stimulation of the resident cells, which acquire the expression of smooth muscle α-actin and increase proliferation rate and ECM synthesis [62]. In cardiovascular tissues, as well as in other regions of the body, the key event during gastrulation, heart formation, but also fibrosis [63], has been long reported to be the epithelial-to-mesenchymal transition (EMT), tightly regulated by TGF-β [64–66]. Currently, the paradigm of EMT as primary cause of cardiac fibrosis is being questioned, since it has been shown that EMT is a rare event in adult fibrotic tissues of the heart. Furthermore, the resident cardiac fibroblasts are directly activated in healing and remodeling responses of interstitial fibrosis [67] and, together with perivascular pericytes, serve as precursors of the myofibroblasts responsible for the fibrotic tissue deposition, as proven by genetic fate mapping studies [68].

2.1. TERM therapeutic solutions for cardiovascular fibrosis

The replacement of the fibrotic tissues with viable and functional biological equivalents is one of the most important aims of cardiovascular TERM, which has been pursued through cell therapy and TE as summarized in Fig. 2.

- Myocardial TERM

Cell therapy, especially based on autologous and allogeneic bone marrow (BM) stem cells, has been tested in animal models and then applied in the cardiology clinics as a promising treatment for acute and chronic ischemia and their fibrotic consequences, by the mitigation of the inflammatory response, the increase of vascularization in the ischemic area and of cardiomyocytes' viability in the penumbra [69–71]. More positive outcomes have been observed at the preclinical and clinical settings with cardiac stem cells, i.e. a quiescent population possibly reactivated by ischemic injury [72–74]. The beneficial effects reached with cell therapy approaches might be, however, limited by the adverse tissue *milieu* of the ischemic heart, i.e. a cytotoxic microenvironment that seriously compromises the viability of the infused cells [69].

In order to effectively restore the damaged contractile function, TE strategies were developed to generate *in vitro* cardiac tissue equivalents, by combining cells with scaffolds and/or other bioactive molecules or by left ventricle restraints [75]. Wang *et al.* developed a combinatorial approach for treating myocardial infarction by injecting an electrically conductive hydrogel loaded with adipose- derived stem cells (ADSCs) and plasmid DNA encoding eNOS (endothelial nitric oxide synthase) nanocomplexes. This resulted in a reduced fibrotic area and a significant improvement of the heart function in a rat model [76].

Paracrine factors secreted by the stem cells (known as secretome) are thought to be responsible for the positive outcomes of cell-based therapies. Based on this notion, Waters *et al.* injected hydrogels (composed of gelatin and Laponite) loaded with ADSC secretome into the peri-infarct region in rats, and observed increased angiogenesis, reduced scar area and cardioprotection [77]. Using a mechanobiology approach that obviates the need for cells or drugs, Le *et al.* fabricated hyaluronic acid-based microrods that provided local biomechanical and biochemical signals to attenuate fibrosis in a rat model of myocardial infarction [78].

Alginate-based approaches for promoting myocardial repair and regeneration have demonstrated great potential, and some implants have reached clinical trials, also for the treatment of patients with advanced heart failure [79–84].

The use of thermoresponsive polymers has allowed the formation of cell sheets of different cell types (e.g. myoblasts, cardiac stem cells and/or EPCs (endothelial progenitor cells), human BM-mesenchymal stem cells (MSCs)), able to promote cardiac repair, reduce inflammatory cell recruitment and decrease fibrosis onset in acute and chronic ischemic settings, in a pressure-overloaded right ventricle and in a xenogeneic model of ischemic cardiomyopathy in the minipig [85–90].

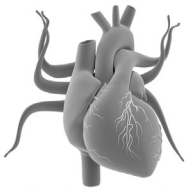
An engineered heart tissue, i.e. a multiple rings-based construct composed of Matrigel and cardiomyocytes derived from rat neonatal hearts [91], revealed no fibrotic reactions and optimal integration after 28 days of implantation in a syngeneic model of cardiac ischemia [92]. More immunotolerable elements, i.e. fibrin and human embryonic stem cells, are now substituting rodent components [93].

For the achievement of totally bioengineered organs, decellularization and repopulation of animal and human hearts have been attempted [94]. Ideally, immunogenic elements, such as the cells and their components, are removed, while the native ECM is maintained unaltered in its composition and distribution, including the original vascular and nervous ECM scaffolding to facilitate recellularization [95,96]. The first successful attempt to decellularize the heart of a mouse was reported in 2008 by Ott and Taylor by whole organ perfusion with detergents [97]. Afterwards, improved decellularization formulas and cell repopulation, as well as upscaling to porcine and human organs were introduced [98,99]. Preliminary trials in a porcine preclinical model of heterotopic transplantation failed for the immaturity of the organ construct and massive thrombotic formations [100]. Further optimizations are, hence, required for a long term evaluation, encompassing also fibrotic potential analysis.

3D bioprinting of whole or partial heart has been recently proposed [101,102]. Cardiac patches and organ-like structures were fabricated exploiting original omental ECM-derived hydrogels, cardiomyocytes differentiated from patient´s induced pluripotent stem cells (iPSCs) and an advanced printing technology enabling vessel network generation [102]. Although conceptually fascinating, the bioinks-driven recapitulation of a whole functional heart complexity (muscle, heart valve apparatus, coronary arterial tree, conduction system, etc.) requires the

Cell type	Main findings/ issues	Refs
MSCs	✓Applied in the clinic with mild results for acute and chronic ischemia and their fibrotic consequences	[71]
Cardiac stem cells	✓Drastic reduction of the fibrotic scar in the CADUCEUS clinical trial	[73]

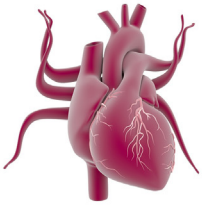
FUNCTIONAL ENDPOINTS:
- Efficient pump performance
- Unidirectionality of blood flow
- Supply of nutrients and oxygen



Fibrotic heart and cardiovascular system

CELL THERAPY

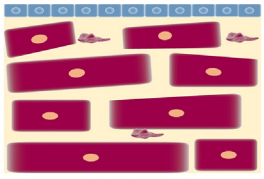
TERM THERAPEUTIC SOLUTIONS FOR CARDIOVASCULAR FIBROSIS



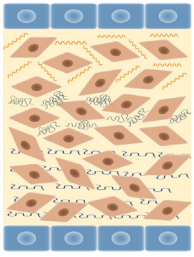
CARDIOVASCULAR TISSUE ENGINEERING

	TE approach	Main findings/ issues	Refs
Myocardial TE	Electrically conductive hydrogel + ADSC + plasmid endothelial nitric oxide gene nanocomplexes	✓Reduced fibrotic area and significant improvement of the heart function in a rat model	[76]
	Hydrogels + ADSC secretome	✓Increased angiogenesis, reduced scar area and cardioprotection in the peri-infarct region in rat	[77]
	Hyaluronic acid-based microrods	✓Local biomechanical and biochemical signals to attenuate fibrosis in a rat model of myocardial infarction	[78]
	Alginate-based approaches	✓Promising results in the clinics	[79-82]
	Cell sheets	✓Promote cardiac repair, reduce inflammatory cell recruitment and fibrosis onset in acute and chronic ischemic settings, as well as in pressure-overloaded right ventricle	[85-90]
	Murine Matrigel + rat cardiomyocytes	✓Integration and vascularization of engineered heart tissues, without fibrotic reactions at 28 days after implantation. For a clinical translation, rodent elements have been substituted by human fibrin and cells	[91, 92]
Whole heart bioengineering	Decellularization of the whole heart	✓Explored for mouse, porcine and human hearts ✓Recellularization represents a challenge ✓Preliminary trials in a porcine preclinical model of heterotopic transplantation failed; optimizations are required	[94, 97-100]
	Bioprinting	✓Applied in vitro with synthetic materials or original ECM-derived hydrogels, combined with cardiovascular differentiated cells. More insights are needed to reproduce a whole, functional heart	[102]
Heart valve TE	Polymeric materials	✓Seeded with cells: Onset of leaflet thickening and fibrosis during in vivo evaluation in animal models ✓Acellular elastomeric valve substitutes demonstrated resistance to fibrosis development and clinical trials are ongoing (Xeltis)	[103-111]
	Natural materials	✓Fibrin-based leaflets underwent tissue retraction in vivo ✓Textile reinforcement enables mitral valve fabrication ✓Small intestinal submucosa utilized to manufacture valve substitutes	[114] [115] [139]
	Decellularized animal and human heart valves	✓Mature specialized ECM to be combined with cells before implantation in a classical TE approach or to be implanted without cells in a guided tissue regeneration approach ✓Positive clinical results with allogeneic conduits, not confirmed so far in xenogeneic settings	[121-127]. [95, 96, 128-138]
Vascular graft TE	Polymeric material	✓Successful clinical application as total cavopulmonary connection in congenital heart defects	[152]
	Decellularized tissue engineered vessels	✓Growth potential demonstrated in lamb model ✓Clinical application	[148] [149,150,153]

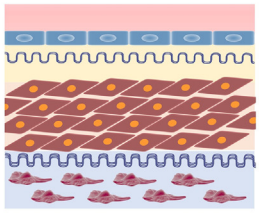
Myocardial tissue



Valvular tissue



Vascular tissue



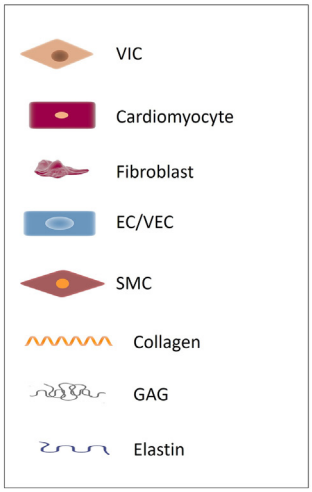


Fig 2. TERM solutions for cardiovascular fibrosis: cell therapy (upper table) and tissue/organ engineering (lower table). The multicellular composition of the cardiovascular tissues (myocardium, heart valve and vessel) are schematically shown (right).

complete insight of all the exact constituting native elements, as well as the understanding of their distributive and hierarchical (sub)molecular relationships, i.e. fundamental knowledge which is still limited nowadays.

- Heart valve TERM

TE strategies to realize a valve have been developed with synthetic and natural scaffolds. The first experiences of heart valve TE (HVTE) relied on valves of polymeric material seeded with differentiated and stem cells of various origin [103–111]. Natural polymers, mainly collagen and fibrinogen, have also been explored [112–120].

Decellularized animal and human heart valve tissues are extensively applied in combination with cells before implantation in a classical TE approach [121–127], or acellular in guided tissue regeneration [95,96,128–138]. HVTE replacements have also been generated by other acellular tissues, such as small intestinal submucosa [139].

Cell-free strategies for heart valve *in situ* TE generally benefit from a more straight-forward production process and offer off-the-shelf availability. This concept has reached preclinical and clinical applications for HVTE based on plain decellularized tissues [95,96,131–134,136,137,140,141]. Recently, promising results have been obtained with valves based on resorbable synthetic scaffolds [111,142], which have led to the first ongoing clinical trials with positive short-term results to date (Xeltis, Xplore-I and Xplore-II trials).

- Vascular TERM

Similarly to HVTE, the field of arterial TE has evolved to reply to the clinical need for functional biocompatible replacements by the combination of analogous components, i.e. synthetic polymers or natural scaffolds, as well as decellularized vessels, eventually seeded with differentiated or more immature cell types [143]. During preclinical evaluation, allogenic decellularized native and TE vessels demonstrated high patency rates and maintained performance, with no signs of fibrosis onset [144–147] and, remarkably, showed the capability to grow in a lamb model [148]. Importantly, tissue-engineered vascular grafts have already reached clinical trials clearly showing the potential of the field [149–152]. In a clinical study with patients affected by end-stage renal disease, human decellularized arteries were evaluated as hemodialysis conduits, acquiring all the characteristics of recipients' blood vessels in terms of physiologic tissue composition and performance [153].

2.2. Cases of fibrosis in cardiovascular TERM

Although the increasing knowledge on the field is facilitating the modeling efforts of biotechnologists, bioengineers and cardiac surgeons, many strategies of cardiovascular TE fail to reconstruct a mature biological replacement due to the occurrence of fibrosis. The onset of this adverse event in cardiovascular TE constructs has a multifactorial nature.

- Fibrosis in myocardial TERM

Myocardial cell-based strategies demonstrated to be generally effective in preventing cardiac fibrosis both preclinically and clinically, apart from the case of less immunotolerated, non-allogeneic mesenchymal stem cell infusion [154,155].

Also in myocardial TE approaches, an unbalance between the immune response and the regenerative effect of a therapeutic TERM strategy is often the main culprit. An emblematic example is related to the use of nano-carbon materials. These are of potential TE interest for heart tissue reconstruction, due to their ability to support the differentiation of electrical and/or contractile cells. However, their non-biodegradable nature prevents their acceptance by the macrophage system, leading to immunogenicity and fibrosis [156].

- Fibrosis in heart valve TERM

The permanent activation of cellular transitions has been described as a cause of tissue thickening and architectural disorganization, often associated with pathological neovascularization [66,157], although their induction has been frequently pursued in HVTE to recreate the complex and multifunctional VIC population of the native heart valve [158].

Unfavorable cell engraftment and uncontrolled differentiation are other triggers of fibrosis in cardiovascular TE. In order to promote homing and maturation of specific cell types, the application of scaffold biofunctionalization seems to offer the best results. Polymers or decellularized ECMs engineered to express/deliver growth factors, antibodies or aptamers have been employed to maximize the adhesion of specific cells, both *in vitro* and *in vivo*, and hence to increase the maturation of the tissue-engineered constructs and minimize the fibrotic risk [159–165]. Flow- and/or strain-based mechanical stimulation of TE cardiovascular constructs also demonstrated to affect cell engraftment and tissue maturation in terms of cytotype differentiation and synthesis of fundamental structural components [166]. In particular, it is fundamental to understand the implications of shear stress, flexure, and/or loading cycles on the sustained activation of fibrotic pathways, as smooth muscle actin upregulation and increased collagen synthesis [167].

The *in vitro* realization of native-like heart valve substitutes by combination of synthetic and/or natural scaffolds and cells is a challenging task. If this process is not opportunely tuned *in vitro*, leaflet shortening and thickening are observed after implantation [103–109,114,168] as a consequence of cell-mediated tissue contraction. Textile reinforcement and mechanical constraint during cultivation have been reported to combat this phenomenon [108,169]. Decellularization of TEHVs has been proposed as a strategy to avoid leaflet retraction by eliminating the contractile activity of the cells. Unfortunately, increased valvular insufficiency developing over time, associated with leaflet shortening, was still reported when decellularized TEHVs were implanted in sheep and non-human primate models [110,170–172]. Recently, Sanders *et al.* proposed an optimization of the cusp design, conceived by means of computational simulations and the valves remained competent *in vitro* for up to about 12 million cycles [108] and in a sheep model until 1 year [173].

This tissue-guided regeneration modality with decellularized native valves has nowadays more than 10 years of clinical experience [174] and new trials are ongoing. In limited cases, the onset of fibrotic responses in implanted decellularized heart valves has been described, as for Matrix P and Matrix P plus tissue-engineered xenogeneic pulmonary valves [130,138] and for Synergraft/ Cryovalve acellular allogeneic/ xenogeneic heart valves [128,135]. The use of a commercial decellularized small intestinal submucosa, i.e. Cormatrix, to fabricate TE valve substitutes was also described as unfortunate in terms of early calcification and fibrosis [139].

- Fibrosis in arterial TERM

The scenario in arterial TE is not dissimilar to the one described for TEHVs and is complicated by the thrombogenic occlusion propensity associated to the smaller vessel diameter. In TERM arterial strategies, the poor maturation of ECM architecture, particularly for polymeric scaffolds, represents a primary reason for mechanical instability, fibrosis and stenosis after implantation [175].

Tissue-engineered arterial patches of polyhydroxyoctanoate (PHA) and P4HB seeded with EPCs and MSCs were implanted in a sheep pulmonary artery model. After 6 weeks *in vivo*, the patches revealed granulation tissue and fibrosis [176].

In a model of transposition of the great arteries, a correction of the supravalvular pulmonary stenosis with autologous pericardium alone or with a bioresorbable patch in a four-layered knitted polydioxanone mesh was attempted. The use of sole pericardium generated a fibrotic reaction [177].

Residual immunogenic potential in xenogeneic decellularized tissues may also be a cause of arterial TERM-associated fibrosis. Decellularized equine carotid arteries demonstrated a fast development of fibrotic tissue after 14 weeks of implantation as cervical arteriovenous shunts [178].

2.3. In vitro models of cardiovascular fibrosis

- Models of myocardial fibrosis

Herum *et al.* created an *in vitro* model of myocardial fibrosis with cardiac fibroblasts and myocytes. The majority of cells responsible for cardiac fibrosis, i.e. mechanically activated cardiac fibroblasts, were induced to proliferate by the paracrine conditioning of stretched cardiomyocytes. They also increased their synthetic activity by direct stretch and by sensing the stiffening of the scarring ECM, and completed their differentiation into fibrosis-inducing phenotypes [62].

Van Spreeuwel *et al.* developed different cardiac fibrosis models *in vitro* by playing with the ratio between cardiac fibroblasts and collagen amount with respect to cardiac myocytes. They observed that the number of cardiac fibroblasts rather than the collagen amount influences contractility of the tissue construct. In fact, a sensible decrease in cell contractions was documented when this population was particularly abundant [179]. In addition, aging has a significant effect on the cross-talk between these two cardiac cell types, with important consequences for TE applications intended for replacement [180].

Contractile tissue constructs realized with gelatin methacryloyl hydrogels, cardiac myocytes and fibroblasts, were shown to react to the exogenous addition of TGF-β1 with the activation of the quiescent fibroblasts and the expression of fibrotic protein markers [181]. In a follow-up study, a microdevice was developed to subject the gels to dynamic mechanical stimulation and investigate its influence on the fibroblast phenotypic transition [182]. The resulting platform represents a promising tool to test new therapeutic strategies for cardiac fibrosis.

More recently, Lee *et al.* established a human cardiosphere-based model of cardiac fibrosis by combining human cardiomyocytes, differentiated from embryonic stem cells, and BM-MSCs, which transdifferentiated into myofibroblasts upon exogenous addiction of TGF-β [183].

- Models of heart valve fibrosis

Merryman *et al.* generated a 2D model of heart valve fibrosis by mechanically stressing ovine VICs derived from both semilunar and atrioventricular valves. To simulate the effects of differential transvalvular pressures occurring in the right and left side of the heart, they imposed micropipette aspiration to the different cell cultures and verified that left-side valve-derived cells responded to the stress by increasing the expression of smooth muscle actin and heat shock protein 27, in addition to enhanced collagen synthesis [167].

Puperi *et al.* proposed a whole 3D model of valvular fibrosis based on electrospun polyurethane and poly(ethylene glycol) hydrogel. By developing a 200 μm-thick scaffold, they could recapitulate a fibrotic valve tissue, in which VICs infiltrated in the stiff mesh by acquiring an activated phenotype after mechanical constraint [184].

In order to understand the cellular mechanisms of aortic stenosis, valve myofibroblasts have been widely studied in 2D cultures by Anseth and her group. In particular, they addressed the ability of TGF-β1 to finely regulate VICs and induce the acquisition of a myofibroblast phenotype. By the application of microarray technology, the progressive phenotypic changes induced by TGF-β1 became unravelled, by identifying a downstream target, i.e. CDH11, that acts as a pathway modulator and/or inhibitor [185]. More recently, they developed a high-throughput cell encapsulation platform to enable the fibrotic disease modeling in 3D settings. Poly(ethylene glycol) hydrogels functionalized with RGDS peptides boosted the activation of VICs in a dose-dependent manner [186].

- Models of vascular fibrosis

In the settings of arterial fibrosis, Butcher *et al.* demonstrated by means of rat aortic smooth muscle cells immersed in Type I collagen hydrogels and submitted to cyclic equibiaxial strain that fibroblast phenotype conversion could be achieved [7].

A rational modeling of tissue development and disease by experimental and computational approaches might fasten the generation of suitable bioengineered equivalents. This has been recently reported for arterial TE and can be extended to other regenerative medicine subfields [187].

An *ex vivo* arterial disease model has been realized by Kural *et al.*, by culturing rat aortas *in vitro* in a dynamic bioreactor system with controlled intramural pressure and shear stress. The initial phases of the atherosclerotic process, encompassing also fibrotic degenerations, were recapitulated after cell injury in the intimal layer [188]. This model enables the investigation of complex atherosclerotic pathomechanisms, by unravelling mechanical, cellular and soluble disease players.

3. Fibrosis in renal TERM

Renal fibrosis is common to all chronic kidney disease, affecting 10% of the world's population and representing a dramatic clinical problem for the current medical practice [189].

As in the cardiovascular tissues, the pathological onset of the fibrotic reaction involves the exacerbate ECM synthesis by myofibroblasts whose origin remains uncertain. A growing body of evidence points to an altered epithelial-mesenchymal crosstalk as a fundamental trigger leading to myofibroblast activation [190] while the role of EMT is a matter of intense debate [190,191]. Again, the TGF-β1 pathway is deemed to be the main player in the activation of renal fibroblasts, their increased expression of contractile proteins and collagen production [192,193].

Similarly to cardiovascular fibrosis, aging has a strong correlation with the onset of fibrotic degeneration in the kidney [194]. Moreover, an important axis between the two organs exists so that epigenetic modifications, i.e. heritable alterations in gene expression, can alter it and favor the progression of fibrosis [195].

3.1. TERM therapeutic solutions for renal fibrosis

Several TERM approaches, comprising cell therapy and replacement solutions, have been proposed to counteract the fibrotic degeneration of the kidney (Fig. 3).

In general, the injection of stem cells (or their secreted microvesicles), progenitors and their genetically engineered version into the failing kidney is a safe and effective procedure for the attenuation of renal inflammation and interstitial fibrosis in animal models of acute and chronic renal diseases [196–206], as well as in clinical settings [204,207]. Besides MSCs, the administration of iPSCs and their derived renal progenitors, obtained also from diseased patients, has shown great therapeutic potentialities for the treatment of fibrosis in renal diseases, by reconstituting 3D proximal renal tubule-like structures or vascularised glomeruli in mouse models of acute kidney injury induced by ischemia/reperfusion [208,209].

The *in vitro* bioengineering of kidneys or of their components offers a potential alternative to allogeneic transplantation when the organ functionality is completely compromised. Still far from a clinical application, several groups have attempted kidney organ regeneration by using either polymeric scaffolds or decellularized ECM combined with different cell types.

In 2002, Lanza *et al.* implanted polymeric tubes with metanephric cells in an animal model demonstrating no fibrosis, and ability to

Cell type/ microvesicles	Main findings/ issues	Refs
MSCs/MSC-extracellular vesicles	✓Pre-clinical studies: attenuation of renal inflammation and interstitial fibrosis in animal models	[197,198, 201- 206]
	✓Clinical studies: improved patients´ renal parameters	[204,207]
iPSCs	✓Pre-clinical studies: successful differentiation to renal progenitor cells, with therapeutic effectiveness in a mouse model of acute kidney injury	[209]

FUNCTIONAL ENDPOINTS:
- Filtration
- Reabsorption
- Secretion
- Excretion
- Urine production

CELL THERAPY

TERM THERAPEUTIC SOLUTIONS FOR RENAL FIBROSIS

Fibrotic kidney

KIDNEY TISSUE ENGINEERING

TE approach		Main findings/ issues	Refs
Kidney decellularization and repopulation		✓Far from clinical application ✓No optimal decellularization method for the kidney available yet	[215]
Renal structures/ organoids	Polymeric tubes + metanephric cells	✓Functional renal units organized into glomeruli- and tubule-like structures able to produce urine-like fluid *in vitro* and *in vivo*	[210]
	Human renal cells + Rat tail collagen Type I	✓Generation of kidney structures *in vitro* ✓Cells survived in the kidney for up to 6 weeks *in vivo*	[211]
	Epithelial and mesangial cells + collagen vitrigel scaffold	✓Reconstruction of a three-dimensional glomerular organoid	[212]

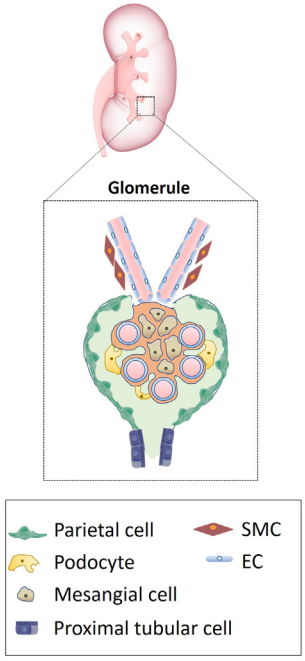


Fig 3. TERM solutions for renal fibrosis: cell therapy (upper table) and tissue/organ engineering (lower table). The multicellular composition of the kidney tissue is schematically shown (right).

produce urine and to remodel into an organized tissue [210]. Similar results were observed with other tissue-engineered constructs, based on natural or polymeric scaffolds and renal cells [211,212]. Some of these approaches will unfortunately find difficult translation into clinical practice due to the use of xenogeneic materials not deprived of immunogenic triggers [213].

Basu *et al.* demonstrated that the conditioned media obtained by the culturing of tissue-engineered renal constructs might moderate the tubulointerstitial fibrosis of the chronic renal disease, by downregulating the TGF-β1 pathway in human proximal tubular cells [214].

In 2010, Nakayama and coauthors attempted as first the whole kidney decellularization [215]. After this experience, new decellularization and repopulation protocols were utilized [216], but information are still missing on the ability of these organ scaffolds to prevent fibrotic reactions *in vivo*.

Hybrid approaches combining synthetic and decellularized materials have been also practiced. After seeding with renal cortical epithelial cells, these *in vitro* bioengineered renal tissues demonstrated ability to reconstruct glomeruli and vascularization in a murine model of partial nephrectomy with no described fibrosis onset [217].

3.2. Cases of fibrosis in renal TERM

TERM strategies are more effective in preventing a further manifestation of fibrosis in renal settings compared to the cardiovascular system. This might be due also to the lower mechanical load to which the kidney and its structures are subjected with respect to the heart.

In a sole case of BM cells infusion, derived myofibroblasts triggered renal fibrosis after injection in the kidney [218].

A case of extensive fibrosis after implantation of an acellular scaffold was described by Osman *et al.* in an experimental replacement of the urethra in the canine model. During *in vivo* follow up, the conduit showed a severe shrinkage and marked narrowing of the lumen. Causes for this degeneration were attributed to the lack of engraftment and vascularization of the decellularized ureteric conduits [219].

3.3. In vitro models of renal fibrosis

Moll *et al.* developed an *in vitro* model of acute tubular injury induced by cisplatin by recreating the tubulointerstitial *milieu* through a 3D culture of human proximal tubular epithelial cells and human dermal fibroblasts in a matrix of type I collagen. Gene expression analysis revealed the crucial regulation of fibroblast phenotype by epithelial cells in the progression to tissue fibrosis [220]. Nugraha *et al.* developed a 3D co-cultured system composed of human kidney tubular cell (HKC-8) spheroids and human renal fibroblasts in order to mimic the renal microenvironment. The proposed system provides a suitable tool for screening of molecules capable to interfere with the crosstalk between epithelial and mesenchymal cells [221].

Takasato *et al.* proposed a nephrotoxicity model formulated with renal organoids. Human iPSCs were differentiated into renal cytotypes by stimulation with CHIR99021 and FGF9 in order to recapitulate the activation of Wnt and FGF pathways, typical of embryonic development. As a result, organoids with distal and proximal nephrons, early Henle loops and glomeruli were generated [222].

Using Organovo's proprietary bioprinting platform, King and colleagues [223] developed a 3D PT ExVive^{TM} Human Kidney engineered tissue, as previously described by Nguyen *et al.* for primary liver tissues

[224]. The complex architecture of the human tubule tissue was recreated *in vitro* by means of a two-step 3D spatial design technique. At first, the basal multicellular interstitial layer was obtained by mixing renal fibroblasts, umbilical vein endothelial cells and NovoGel® Bio-Ink. Then, a polarized renal epithelial monolayer was generated by seeding proximal tubule epithelial cells onto the tissue-engineered constructs 3 days after bioprinting. These engineered tissues were valid models both for cisplatin nephrotoxicity assessment and to mimic renal fibrosis. As evidenced by the authors, kidney TE approaches based on differentiated cells for the construction of multicellular and complex organoids are likely endowed with superior potential to recapitulate the physiology and pathophysiology of the renal fibrotic tissue in comparison to the procedures relying on more immature cells, such as stem cells. In addition, these platforms can be applied to test new therapeutic solutions for renal fibrosis prevention. As previously mentioned in section 3.1, the conditioned medium of renal engineered tissues induced TGF-beta pathway downregulation [214], possibly by the multifactorial effect of cytokines and microvesicles.

Microfluidic devices are gaining increasing attention in the modeling of renal diseases. In these organ-on-a-chip solutions, kidney epithelial cells are seeded onto molded polydimethylsiloxane or porous microfluidic channels, including hydrogels [220,225–227]. These 2D and 3D systems are able to offer cell culture conditions similar to the ones occurring naturally, thus simulating the real shear stress sensed by renal epithelial cells.

As recently pointed out by Desrochers *et al.* [228], only few kidney engineered models allow for long periods of *in vitro* follow-up and 7 days are usually the maximum observational time. For kidney disease with chronic progress, this duration is insufficient to reveal the development of the classical signs and to evaluate the effects of any drug treatment.

In the quest for a personalized medicine approach, *in vitro* tissue-engineered models based on patient's own cells are more and more indispensable. Obtaining cells by means of invasive harvesting procedures represents a clinical and ethical challenge for high-risk patients. In this regard, iPSC differentiation technology is attracting a great deal of interest. Indeed, recent advances in directed differentiation protocols have enabled the generation of kidney organoids [229,230] with great potential as *in vitro* fibrotic disease models [231].

4. Fibrosis in pulmonary TERM

Pulmonary fibrosis is characterized by the deposition of excessive ECM in the interstitium of the lung and it is a feature of different lung diseases with diverse etiology. Pulmonary fibrosis of unknown etiology is termed idiopathic pulmonary fibrosis (IPF). IPF results in the progressive destruction of the lung and it has a poor prognosis, with a median survival of 2-4 years after diagnosis and a mortality rate exceeding that of many cancers [232,233]. Up to 18 cases per 100000 people are diagnosed annually in Europe and North America [233,234]. IPF is more common in men and is rare in people younger than 50 years (median age at diagnosis is about 65 years) [233]. It has been considered a chronic inflammatory disorder that progresses to fibrosis. However, it is now generally accepted that it is a consequence of multiple interacting genetic and environmental risk factors, with repetitive injuries to ageing alveolar epithelium in genetically susceptible individuals [233,235]. Chronic dysregulation of type 2 alveolar epithelial cells (AEC2s) is thought to be central. Repetitive micro-injuries initiate aberrant epithelial–fibroblast communication and the activation of matrix-producing myofibroblasts which results in ECM accumulation and remodelling of lung interstitium [233].

Lung disease management consists of multimodal drug therapies, rehabilitation and surgical interventions (e.g. lung volume reduction and airways-stenting). FDA approved recently two drugs for the treatment of IPF [3,236,237], pirfenidone and nintedanib, which have shown to reduce disease progression and represent a clear improvement with respect to previously used ones. Although they do provide hope that IPF can be treated, their clinical efficacy is controversial, the therapeutic effects are small and they come with side effects [3]. Furthermore, the high costs are likely to prevent a widespread use of these drugs [238].

Lung transplantation is, therefore, still indicated as the only effective therapy with proven benefits. The donor shortage, the organ's quality and transplantability, the fact that not all patients are transplantation candidates, the life-long immunosuppression, the risk of graft rejection are critical issues and the wait-list mortality remains a concern [238–240].

4.1. TERM therapeutic solutions for pulmonary fibrosis

TERM solutions are presented in Fig. 4.

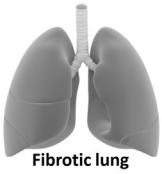
Creating functional lungs could be a valid answer to the urgent unmet need for lung transplantation and increasing effort has been dedicated in the TE field to this challenge. The lung is an extremely complex organ because of the diverse cellular composition, the 3D architecture, the ECM with regional-specific cues for cellular adhesion and the functions it needs to perform. Perfusability and gas exchange without edema are the minimal functional requirements for a bioengineered lung. In the native healthy organ, the alveolar-capillary interface is estimated to correspond to a 70-100 m^2 surface area [239]. This, together with the variety of the cell types and their number, gives already an idea of the remarkable challenge that scientists face. Furthermore, to be functional *in vivo*, an engineered lung should contain lung-specific cells, display the branching geometry of the airways and have mechanical properties that allow ventilation at physiological pressures, as formulated by Niklason and colleagues [241].

Attempts to engineer *de-novo* a lung starting from synthetic and natural polymers have been performed. Formation of alveolar-like structures were shown in 2D and 3D constructs, however gas exchange capabilities are rarely tested. With this respect, it is worth mentioning the work of Hermann *et al.,* which showed the formation of alveolar-like barriers with intracellular junctions on both the epithelial and endothelial sides and gas exchange [242]. Although interesting results have been obtained with these strategies, they addressed only some features of the alveolar architecture and were not able to reproduce a hierarchical airway and alveolar network with its corresponding vasculature. This precludes host-driven ventilation, perfusion and gas exchange over a large surface area, thus clinical applicability. So far, the only approach to produce whole organs is lung decellularization [240,241,243]. However, recellularization to gain functionality is a major issue, considering that more than 40 cell types [239,240] are responsible for the lung's functions, which, besides oxygenation and ventilation, include mucocilliary removal of airborne debris, immune system regulation and control of airway fluid balance. It is clear that recellularization of human lungs cannot be achieved with primary somatic lung cells. The use of stem and progenitor cells has been proposed as a potential solution. The decellularized lung ECM of lungs is potentially capable of regional specific cellular differentiation, likely in a tissue-specific way. Endothelial progenitor cells (EPCs) and MSCs isolated from peripheral tissues (e.g. BM and fat) have shown promising results towards the recapitulation of functional features of lungs by differentiation into pulmonary vascular endothelial and alveolar epithelial cells. As for other organs, the progress in iPSCs technology is of fundamental importance to [244–246].

Besides the 3D architecture and the molecular cues that the substrate provides, the mechanical forces have a critical influence on cellular differentiation and function. Therefore, the development of bioreactors able to recapitulate the main physiological loads has received great consideration, from the microfluidic scale to the human-sized whole lung systems. Bioreactors can also support defining strategies to optimize *in vitro* recellularization [247,248]. Being able to position specialized cells in the correct anatomical location remains a

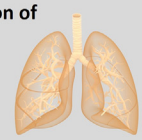
Cell type	Main findings/ issues	Refs
MSCs 	✓Clinical trials have shown safety of allogenic placenta- and BM-derived MSCs delivery to IPF patients	[255,256]
	✓The time of delivery is a crucial parameter and the risk of fibrosis worsening has increased caution in the use of MSCs	[21,250, 253,254]

CELL THERAPY



TERM THERAPEUTIC SOLUTIONS FOR PULMONARY FIBROSIS

LUNG TISSUE ENGINEERING

TE approach	Main findings/ issues	Refs
Co-culture system of human distal lung epithelial cells and human microvascular endothelial cells	✓Alveolar-like barriers	[242]
Decellularization of the whole lung 	✓Feasibility shown for human lungs ✓Recellularization represents a challenge	[241,243]

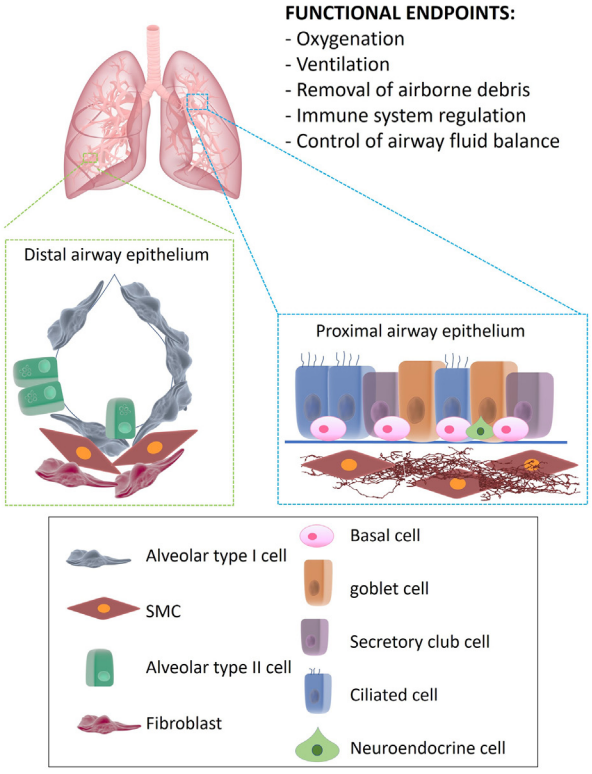


Fig 4. TERM solutions for pulmonary fibrosis: cell therapy (upper table) and tissue/organ engineering (lower table). The multicellular composition of the lung tissue is schematically shown (right).

major area of investigation, where a wide range of aspects needs to be carefully considered.

Also in the case of IPF, cell therapy has great potential as treatment option [249]. Various animal studies have delivered promising results and cell therapy for IPF has reached clinical trials. MSCs are thought to contribute to alveolar epithelial regeneration through secretion of paracrine mediators [238,250,251]. The therapeutical potential of MSCs has been investigated in the mouse bleomycin-induced IPF, as reviewed by Toonkel *et al.* [252]. Encouraging results have been reported when MSCs were delivered during the acute injury phase; however, the time of delivery seems to be a crucial parameter and the possibility of worsening the fibrosis has led several authors to ask for caution in the use of MSCs [21,250,253,254]. Clinical trials have so far shown safety of allogeneic placenta- [255] and BM- [256] derived MSCs delivery to IPF patients. Other phase I/II trials are ongoing, including one where autologous lung stem cells are used [238]. Future studies to determine efficacy are warranted. A number of questions have already been raised with respect to which MSCs source is the most efficacious, how to handle the cells in the lab, which administration route should be used (e.g. endobronchial vs intravenous), cell number, number and frequency of doses to be delivered [257].

4.2. Cases of fibrosis in pulmonary TERM

Implantation of recellularized lungs has been reported in rodents with the goal of demonstrating gas exchange, one of the main functions that must be recapitulated. These studies had limited durations (45 minutes to 6 hours) and did not allow any evaluation of the implants in terms of fibrotic response [241,243]. The bioengineered grafts failed because of edema, secretions and thrombus formation. In a following study, decellularized rat lungs were seeded with immature rat lung cells and human umbilical cord endothelial cells and conditioned *in vitro* with *ad hoc* bioreactors. The grafts were orthotopically transplanted, perfused by the recipient's circulation, ventilated through the recipient's airway and provided gas exchange *in vivo* for 7 days. During the subsequent 7 days, the performance of the lungs declined and consolidation and inflammation were reported [258]. Pleural fibrous scar tissue was seen in all the implanted recellularized grafts, which restricted lung expansion. The authors reasoned that the formation of this tissue might be a preserved recipient natural killer cell response of the athymic nude rats to the implanted material, which was mainly obtained from Sprague-Dawley rats. A host response to the incomplete recellularization was hypothesized by the authors as cause of the increased number of macrophages seen across the graft area at explantation. Further causes were identified in the compromised clearance mechanism and chronic infection in the bioartificial lung. Release of proinflammatory cytokines may drive the increase in resident MSCs. These cells are, on one hand, thought to contribute to epithelial repair and regeneration, but, on the other hand, to be responsible for the development of interstitial fibrosis [258,259].

Also for MSC transplantation in the lungs, as in the case of the liver, concern that some subpopulations can participate in fibrosis progression has been raised [21,250,260]. Epperly *et al.* demonstrated that cells of BM origin contributed to the pathophysiology of murine irradiation-induced pulmonary fibrosis. They showed that GFP-labeled BM-MSCs that were systemically injected were found in the fibrotic lesions and coexpressed vimentin, suggesting a fibroblast phenotype. [260].

Yan *et al.* showed that Flk-1(+)MSCs injected into the lung immediately after irradiation were able to differentiate into functional lung cells. However, when injected two months after irradiation, in the established fibrotic phase, they were mostly located in the interstitial area and assumed a myofibroblast phenotype. This suggests that these cells would be involved in fibrosis development. The authors explained this result by the influence of the changing microenvironment on the cell differentiation. The critical importance of the time of injection with respect to the disease progression was also pointed out by Ortiz *et al.* in a bleomycin mouse model. They showed that early

(immediately after bleomycin challenge) but not late (7 days after bleomycin challenge) administration of MSCs reduced the degree of inflammation and fibrosis in the lungs. Although low levels of MSCs engraftment were reported, they had a positive outcome. This could be explained by the fact that MSCs differentiated into epithelial type II cells and, in this way, partially restored the stem cell pool, thereby recovering the disrupted alveolar surfaces and augmenting the repair process. Alternatively, the authors suggested that MSCs may alter the microenvironment of lung at sites of engraftment by producing cytokines that disrupt signalling pathways leading to fibrosis. Engraftment of cells delivered 7 days after injury was not inhibited, however the cells were not able to alter the course of disease progression [20].

4.3. In vitro models of pulmonary fibrosis

It is extremely challenging to create *in vitro* models of the lung able to recapitulate all components and functions. *In vitro* systems of varying complexity have been proposed, starting from simple monolayer cultures to co-cultures on transwell inserts [261] or tailored electrospun biomimetic membranes [262,263], to a more sophisticated microfluidic lung-on-chip device [264–266], tissue-engineered bronchiole [267] and airway wall [268]. A main topic of interest is the recreation of the alveolar-capillary barrier in models that can be used for drug screening and research on asthma, chronic obstructive pulmonary disease, lung granulomas, pneumonia and pulmonary edema [269].

Less frequent is the introduction of fibroblasts in the co-culture, a crucially important component in a fibrosis model [267,268]. Miller and colleagues tissue-engineered a cylindrical construct composed of ECM and human lung primary cells (fibroblasts, airway smooth muscle cells, small airway epithelial cells) and subjected it to radial distension and air flow in a bioreactor. This model enabled investigation of cell-cell interactions and airway remodelling [267] and, although not specifically tested with respect to its capability to recapitulate onset or progression of fibrosis, it is in principle suitable for such studies.

Interestingly, acellular diseased lungs have been proposed as *in vitro* models for studying cell-ECM interaction in a disease-specific manner [23,270]. Booth and colleagues obtained sections of decellularized human normal and fibrotic lungs and seeded them with fibroblasts. They showed that the fibrotic ECM promoted myofibroblast differentiation compared to the normal ECM, showing the potential of the *in vitro* system to investigate matrix contributions to lung pathology in a disease-specific manner [23].

Wagner and colleagues further developed the concept of using a decellularized matrix as *in vitro* system by developing 3D scaffolds for high-throughput studies of lung disease and regeneration. They excised small segments of acellular human and porcine scaffolds including airways and vasculature, which could be used for selective inoculation of cells. Furthermore, the authors developed a synthetic pleural coating to obtain isolated lung units. These units were subsequently sectioned in thin slices for high-throughput and long-term culture [271].

Recently, McCauley and colleagues were successful in obtaining airway epithelial organoids from human iPSCs by stage-dependent modulation of Wnt signalling pathway in a manner that recapitulated *in vivo* development. In this way, the authors could influence cell fate decisions towards proximal airway versus distal alveolar epithelial patterning. They could then produce airway organoids from cystic fibrosis patient-specific iPSCs lines before and after gene editing to correct the CFTR genetic lesion responsible for cystic fibrosis. The organoids exhibited CFTR-dependent swelling in forskolin-induced epithelial sphere swelling assays. Although demonstrated for the case of cystic fibrosis, this model offers potential clinical benefit for precision drug screening and regenerative medicine also for other diseases of the airways [272].

5. Fibrosis in hepatic TERM

Liver fibrosis is a wound healing response characterized by the damage to hepatocytes and the accumulation of ECM rich in fibrillar collagen (scar tissue), as a result of various types of persistent injury. Virtually all chronic liver diseases result in fibrosis, which can progress to its end-stage form (cirrhosis) and hepatocellular carcinoma. Viral infection (hepatitis B and C), alcohol abuse and metabolic syndromes due to obesity, and diabetes are common causes of fibrosis. In liver cirrhosis the hepatic tissue architecture and the blood flow are severely compromised, ultimately leading to liver failure. Cirrhosis is responsible for 170,000 deaths in Europe [273,274], and over one million worldwide [275]. Liver cancer causes 47,000 deaths each year in Europe [273]. The only curative treatment for cirrhosis is liver transplantation, which however, as for other organs, is strongly limited by donor shortage.

5.1. TERM therapeutic solutions for hepatic fibrosis

Much research effort has been dedicated to the development of cell-based therapies as alternative options to liver transplantation as summarized in Fig. 5.

Cell transplantation aims at stimulating endogenous regeneration by providing functional hepatocytes. Traditionally, human primary hepatocytes have been used in this approach and positive results have been shown in animals and patients with acute liver failure and metabolic disorders [276–279]. However, the limited availability of human hepatocytes, their tendency to lose functionality when removed from the hepatic microenvironment, their poor *in vitro* proliferation, the difficulty to achieve functional long-term engraftment and the immune reaction risk have pushed researchers to seek alternative cell sources. The use of MSCs from several human tissues (BM, adipose tissue, umbilical cord (blood and matrix), Wharton's jelly, dental pump, placenta), iPSCs and induced multipotent progenitor cells, as well as the direct reprogramming of somatic cells *in vitro* and *in vivo* have been reported [280,281].

MSCs, besides being able to differentiate into hepatocyte-like cells, are capable of immunomodulation, trophic paracrine activity and homing to the site of injury [282,283]. These properties have made them the most promising cells for the treatment of liver disease [281,284,285] and benefits have been demonstrated in clinical trials [286,287]. However, concerns for the use of MSCs have been raised because of their tumorigenic risk [288–290] and their fibrogenic potential [291,292].

Liver TE has the goal of reproducing the organ *in vitro* to restore or replace the diseased one. Many models of hepatic tissue have been proposed. However, only few approaches have reached the stage in which the potential for hepatic function could be shown *in vivo*, i.e. for whole organ decellularization [293–298], liver organoids/buds [299,300] and sheets [301]. Also in the case of the liver, the capability of properly repopulate the acellular ECM is of crucial importance for the implant's success and represents a challenge because of the cellular heterogeneity and the high cell numbers needed [280].

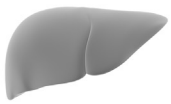
Takebe and colleagues demonstrated *in vitro* self-condensation of 3D fetal liver-like buds starting from a 2D culture of human iPSC-derived hepatic cells, human umbilical vein endothelial cells and human MSCs. The vasculature formed within the buds anastomosed with the host vessels within 48 hours after implantation in a mouse model and the functional vasculatures stimulated the maturation of iPSC-buds into tissue resembling the adult liver [299,300].

Recently, cell sheet engineering has been used to fabricate scaffold-free layers of iPSC-derived hepatocyte-like cells *in vitro*, which were then positioned on the injured liver of mice [301]. The study revealed cellular engraftment and liver-specific protein production. In addition, the human sheet transplantation could efficiently rescue mice from carbon tetrachloride-induced lethal acute liver injury. Remarkably, fine murine vascular structures were formed in the human sheet, suggesting the feasibility of implanting thicker, multilayer sheets in future experiments.

Cell type	Main findings/ issues	Refs
Human hepatocytes	✓Positive outcomes in animals and patients ✓Difficult to obtain/ limited availability	[276-279]
MSCs	✓Attenuation of liver fibrosis in preclinical studies	[281-285]
	✓Improved liver function in clinical trials	[286,287]

FUNCTIONAL ENDPOINTS:
- Bile production
- Metabolism of fat, carbohydrates, proteins
- Vitamin and mineral storage
- Blood filtration
- Immune activity by Kupffer cells
- Albumin production
- Angiotensinogen synthesis
- Clearance

CELL THERAPY



Fibrotic liver

TERM THERAPEUTIC SOLUTIONS FOR LIVER FIBROSIS

LIVER TISSUE ENGINEERING

TE approach	Main findings/ issues	Refs
Cell-sheets	✓Layers of iPSCs-derived hepatocyte-like cells in vitro revealed cellular engraftment and liver-specific protein production when applied on the injured liver of mice	[301]
Liver organoids/ buds	✓Cultures of iPSCs-derived hepatic cells, human umbilical vein endothelial cells an human MSCs resulted in tissue resembling the adult liver	[299,300]
Decellularization of the whole liver	✓Recellularization represents a challenge ✓Establishment of a functional vasculature	[293-298]

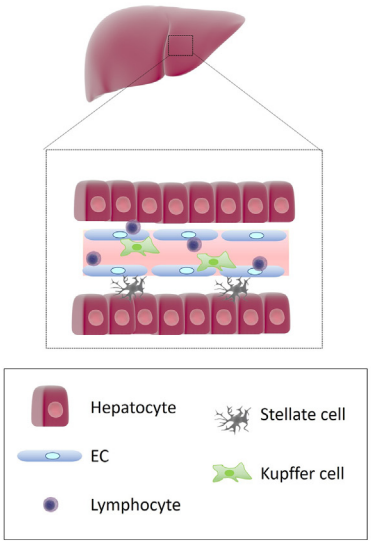


Fig 5. TERM solutions for hepatic fibrosis: cell therapy (upper table) and tissue/organ engineering (lower table). The multicellular composition of the liver tissue is schematically shown (right).

5.2. Cases of fibrosis in hepatic TERM

Baertschiger and colleagues reported MSC differentiation into myofibroblasts with development of fibrous tissue when transplanted into an injured or regenerating liver [291]. Another study showed that human MSCs transplanted into a murine model of acute liver injury rarely differentiated into hepatocyte-like cells while a significant number exhibited a myofibroblast-like morphology [292]. In a careful analysis of data available from preclinical and clinical studies involving MSC-based therapies, Meier and colleagues postulated that there might be various MSC subpopulations with opposite effects and suggested that the conflicting data on the efficacy of MSCs transplantation might be explained with the different MSCs isolation and culture protocols, which probably affect cells' plasticity and function [302]. Indeed, a significant proportion of myofibroblasts in the fibrotic liver is of BM-MSC origin in mice transplanted with sex-mismatched BM [303], as well as in patients who received either sex-mismatched liver or BM transplants [304].

Furthermore, myofibroblastic transdifferentiation of the transplanted MSCs may be induced by the route of injection as well as by the recipient. Importantly, the treatment timeframe might also be crucial with respect to engraftment rate and effects on liver fibrosis because of the changing microenvironment of the injured organ: when injected during the damage phase, the MSCs may directly participate to fibrogenesis while they might accelerate healing during the resolution phase [302,305].

5.3. In vitro models of hepatic fibrosis

The liver is a critically important organ for pharmaceutical testing as the response to a given drug is often determined by its hepatic metabolism. Drug-induced liver injury is the leading cause of withdrawal of potential therapeutical agents from human clinical trials or even from the market. 90% of newly developed compounds fail during clinical trial with one third of such failures being attributed to organ toxicity. Because of important species-specific differences in drug metabolism pathways, only 70% of compounds that are toxic in humans are identified in animal testing, with the percentage going as low as 43% when rodent models are used. The low number of new chemical entities reaching marketing stage is associated, as a consequence, with high costs (2.6 billion US$ per drug, including expenses for the failed products) besides requiring a long time (12-15 years). It is clear that *in vitro* liver models able to predict toxicity would be of extreme value.

To this end, a wide variety of models has been developed ranging from microsomes and 2D hepatocyte monocultures to more complex 3D multicellular structures, as thoroughly described in recent reviews [42,306–309]. Although some of these systems have the potential to act as fibrosis models, only a few of them have been actually tested for their capability of recapitulating aspects of liver fibrosis, such as the activation of stellate cells as a consequence of hepatocyte damage [49]. One example is a bioprinted 3D liver tissue comprising primary hepatocytes, hepatic stellate cells, and endothelial cells, which recapitulated drug-, chemical, and TGF-beta1-induced fibrogenesis at the cellular, molecular, and histological levels [224,310]. Leite *et al.* developed 3D hepatic organoids made of functional hepatocyte-like cells and primary human stellate cells. The spheroids were cultivated in 96-well plates over 21 days and, upon exposure to fibrotic drugs, they demonstrated fibrotic features such as stellate cells activation, collagen secretion and deposition [311]. Coll *et al.* followed a similar approach but used iPSC-derived human stellate cells, which in the 3D spheroids exhibited a quiescent phenotype but mounted a fibrogenic response and secreted procollagen in response to known stimuli and hepatocyte toxicity [312]. Prestigiacomo and colleagues developed an even more sophisticated 3D model by introducing macrophages, as key players in liver fibrosis together with hepatocytes and stellate cells. Human cell lines

representing hepatocytes, Kupffer cells and stellate cells were co-cultured in scaffold-free 3D microtissues and were treated with pro-fibrotic compounds for up to 14 days. The model was able to recapitulate hepatocellular injury, antioxidant defence response, activation of Kupffer cells and of stellate cells, leading to ECM deposition [313]. Feaver *et al.* realized an organotypic liver system that incorporates hepatic sinusoidal flow, transport, and lipotoxic stress risk factors (e.g. glucose, insulin and free fatty acids) with co-cultured primary human hepatocytes, hepatic stellate cells and macrophages. The authors demonstrated that fibrogenic activation markers increased with lipotoxic conditions, including secreted TGF-β, ECM gene expression, and stellate cells activation. The developed system allowed culture in near-physiological insulin/glucose *milieus* and exhibited drug responses at clinically relevant concentrations [314,315]. Miyauchi *et al.* used decellularized fibrotic model livers from CCl4-treated rats with a distorted ECM microstructure as scaffolds for hepatocellular carcinoma (HCC) cells. They observed an EMT, increased proliferation and chemoresistance of the HCC cells, demonstrating the effect of fibrotic ECM on the malignant behaviour of these cells [316].

6. Conclusions

The general lack of efficient therapies for fibrosis and the high incidence of the disease have stimulated great scientific effort in finding new clinical solutions. The challenge is enormous, with almost 45% of deaths in the developed countries being attributed to fibroproliferative diseases [2]. The unmet need for transplant organs is estimated in millions per year in the USA and Europe (when all diseases potentially addressable by organ replacement are considered) [317] and the drug discovery process suffers from the lack of appropriate preclinical models of fibrosis pathophysiology and the consequent very high failure rates [25].

The application of TERM strategies has contributed to remarkable advances in the identification of therapeutic answers to this clinical need. The approach of cell delivery to the fibrotic tissues has already been implemented in the clinical settings, showing moderate abilities to prevent disease progression and restore organ's functionality. Bioengineered organs could be a replacement option to overcome the donor shortage and solve one of the major challenges in medicine today. Despite being still in its infancy, the *de novo* creation of functional complex whole organs is showing promising preclinical outcomes. The state-of-the-art of *in vitro* fibrosis models includes TERM approaches, as the generation/application of (i) 3D scaffolding, (ii) bioreactors, (iii) stem cells, (iv) decellularized ECMs and (v) organoid technology. They are not yet able to fully recapitulate fibrosis, but have opened the scenario of humanized platforms for toxicology screening and drug testing towards effective personalized clinical therapies.

Fibrosis presents common features across different organs such as the activation of myofibroblasts, histomorphological changes, tissue stiffening and similar signalling pathways (i.e. TGF-β, MAPK, and PDGF activation), which support the idea of antifibrotic therapies effective for multiple organs. For example, inhibition of TGF-β1 ameliorated fibrogenesis in fibrosis models involving skin, liver, kidney, lung, and heart, but its pleiotropic effects limit the safety of its systemic administration. On the other hand, the environmental factors, the cellular composition and the regenerative capacity of the parenchymal cells are organ-specific. Triggers can also be associated with a specific organ, as, for example, viral infections, which are a cause of fibrosis for the liver, but not for the heart, the lung and the kidney. The liver is, by far, the organ that motivated more optimism in the treatment of fibrosis as it shows reversal of advanced states of the pathology. The cardiomyocytes, contrary to the hepatocytes, display a very limited regenerative capability. A further difference is the association between cancer and fibrosis that exists for lung but not for kidney and heart, while liver cirrhosis is considered a precancerous stage [318].

The organ specificity is crucial for TERM therapies relying on cell differentiation and organ engineering, as well as for *in vitro* models. Besides the requirement for the cell types and numbers, it directs the choice of fabrication technique, the definition of mechanical conditioning and even the overall regenerative strategy. Complex tissue architectures require more sophisticated techniques, as for example multiple heads-3D bioprinting, to selectively position different cells and materials in a controlled structure (e.g. for kidney, myocardium), while other tissues can be recapitulated with classical techniques like moulding (e.g. heart valves and vascular grafts). Substitutes with a primarily mechanical function, such as heart valves and vascular grafts, can be implanted directly without any prior cell seeding, as proposed by the *in situ* tissue engineering approach, while other organs like kidney, lung and liver rely mainly on the cellular components, which need to be functionally organized at the moment of implantation. Heterogeneity and high numbers of cells represent demanding requirements for effective organ reconstruction. To this end, the advances in differentiation of MSCs and, especially, iPSCs into precise phenotypes are crucial to make the concept of tissue-engineered organs feasible. Furthermore, the availability of specific cells in large numbers would support the development of bio-assisted extracorporeal devices, which represent another interesting TERM application in cases of fibrosis. This includes endothelialisation of artificial lungs [319–321] and ventricular assist devices [322], the epithelialization of artificial kidneys [323–325] as well as the incorporation of hepatocytes in artificial livers [284,326–337].

While sharing the general enthusiasm that drives the TERM field, we also pointed out the concerns raised from some controversial aspects, such as the triggering of a fibrotic response by a regenerative approach and the sometimes contradictory outcomes of different studies on stem cells delivery. In order to develop effective therapeutic TERM strategies, these points need to be addressed by i) further advancing the ability to tune the immunomodulatory properties of the implants; ii) clarifying the role of the microenvironment of injured/pathological organs (e.g. ECM, stiffness, inflammation, vascular damage, oxidative stress); iii) standardizing protocols to obtain robust clinical data on cell therapy (e.g. cell sources, isolation, culture conditions, doses, frequency and timeframe of administration); iv) further developing and validating 3D biomimetic *in vitro* models.

Future progress and convergence of many different scientific areas such as cell engineering, mechanobiology, genome editing, biomaterials science, bioreactor and biofabrication technologies will enable next-generation TERM solutions, endowed with the effective potential to tackle more efficiently the battle against fibrotic diseases.

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Declaration of interests

All authors declare no competing interests.

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