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Citation for published version (APA):

Smits, A. I. P. M., & Bouten, C. V. C. (2018). Tissue engineering meets immunoengineering: prospective on personalized in situ tissue engineering strategies. *Current Opinion in Biomedical Engineering*, 6, 17-26.
<https://doi.org/10.1016/j.cobme.2018.02.006>

Document license:
TAVERNE

DOI:
[10.1016/j.cobme.2018.02.006](https://doi.org/10.1016/j.cobme.2018.02.006)

Document status and date:
Published: 01/06/2018

Document Version:
Publisher's PDF, also known as Version of Record (includes final page, issue and volume numbers)

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
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Tissue engineering meets immunoengineering: Prospective on personalized *in situ* tissue engineering strategies

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Abstract

For many applications, tissue engineering strategies are increasingly moving from an *in vitro* to an *in situ*-driven approach. This innovative strategy employs readily-available, resorbable scaffolds, designed to induce endogenous tissue regeneration directly *in situ*. Therein, one of the main challenges is the regeneration of functional new tissue, rather than fibrotic scar tissue, for which harnessing and directing the host immune system is paramount. In this concise review, we address the most important recent findings with respect to immunomodulatory strategies, considering both the scaffold-dependent factors (e.g. material composition, microstructure) and scaffold-independent, patient-specific factors (e.g. age, comorbidities). Moreover, we reflect on the necessity of adequate models to truly grasp a fundamental understanding of the immunological processes underlying regeneration in a clinically relevant context.

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Current Opinion in Biomedical Engineering 2018, 6:17–26

This review comes from a themed issue on **The Future of Tissue Engineering**

Edited by **Leda Klouda, Katja Schenke-layland and Carlijn Bouten**

Received 1 February 2018, revised 27 February 2018, accepted 27 February 2018

<https://doi.org/10.1016/j.cobme.2018.02.006>

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Keywords

Immunomodulatory scaffolds, Macrophages, Regenerative medicine, Biomaterials, Foreign body response, Inflammation.

Abbreviations

TE, tissue engineering; FBR, foreign body response; DAMPs, damage-associated molecular patterns; PRRs, pattern recognition receptors; IL-8, interleukin-8; ROS, reactive oxygen species; MCP-1, monocyte chemoattractant protein-1; FBGCs, foreign body giant cells; VEGF, vascular endothelial growth factor; ECM, extracellular matrix; SIS, small intestine submucosa; PCL, poly(ϵ -caprolactone); PLGA, poly(lactic-co-glycolic acid); NETs, neutrophil extracellular traps..

Introduction

Traditionally, the three main components of tissue engineering (TE) strategies have been scaffolds, cells and conditioning (e.g. biomechanical, biochemical); aiming to replicate or mimic the sophisticated composition, structure and function of native, living tissues in order to replace their native counterpart when irreversibly damaged. Notably, this TE trinity does not directly include the intended patient, or any of his/her characteristics. By no means is this trivial, as the response of the body to a TE construct is arguably the most critical determinant of the success or failure of integration and long-term functionality of a TE construct upon implantation. Any TE implant, whether or not it is immunogenic, will trigger an inflammatory response upon implantation into the body, ignited by the tissue damage that inevitably occurs due to the implantation procedure. As such, attempting to replicate the native tissue in all its aspects *in vitro* as a ready-made, biomimicking product at the time of implantation may not be the best strategy to ensure optimal long-term functionality *in vivo*. Rather, a TE construct has the highest chance of success if it is optimally integrated and remodeled by the body itself after implantation.

Hence, the development of bioinstructive immuno-modulatory TE scaffolds, which are designed to trigger a favorable endogenous regenerative response upon implantation, has taken the stage in state-of-the-art TE strategies for a variety of applications (a concise selection of which is presented in [Table 1](#)). This is reflected by the transition from a predominantly *in vitro* to an *in situ* centered TE approach. *In situ* TE employs off-the-shelf available, resorbable grafts, which are remodeled by the recipient into an autologous, living tissue, directly in the tissue's functional site. The transition from *in vitro* to *in situ* TE does not mean the original TE trinity no longer applies. Rather, the aforementioned basal elements of scaffolds, cells and engineering should be viewed upon in a different context, orchestrated by the patient and the patient-specific characteristics. Therein, the role of the scaffold is twofold: (1) taking over the function of the replaced tissue in the initial phases after implantation, and (2) providing a favorable niche for host cells to populate, differentiate and build up new functional tissue. Scaffolds for *in situ* TE can be of natural origin (e.g. decellularized native tissues, *de novo* engineered decellularized tissues or prefabricated out of natural materials) or synthetic origin, or a combination of both (i.e.

Table 1

Concise selection of recent studies demonstrating the *in situ* tissue engineering principle for various applications.

Application	Scaffold type	Ref.
Blood vessels	Composite resorbable synthetic grafts coated with tropoelastin	[1]
	MCP-1-eluting microfibrinous PCL grafts	[2]
AV-shunt	Decellularized <i>de novo</i> engineered matrix	[3]
	Autologous <i>in vivo</i> engineered fibrous capsule via FBR	[4]
Heart valves	Resorbable microfibrinous supramolecular elastomer	[5]
	Decellularized <i>de novo</i> engineered matrix	[6]
Cartilage	Composite PCL/HA scaffolds $\pm$ TGF- β_3	[7]
	Chondroitin sulfate functionalized collagen scaffold	[8]
Myocardium	Microfibrinous elastomeric mesh + ECM digest gel	[9]
Bone	Decellularized bone functionalized with IFN- γ + IL-4	[10]
Nerve	Agarose filled polysulphone channels loaded with fractalkine or IL-4	[11]
Hernia repair	Microfibrinous elastomeric mesh + ECM digest gel + NO2-OA	[12]
	Resorbable microfibrinous supramolecular elastomer	[13]
Bladder	Collagen-heparin scaffolds loaded with various growth factors	[14]
Muscle	Various ECM-based matrices	[15–17]
Skin	Hydrogel functionalized with Substance P	[18]

MCP-1, Monocyte Chemoattractant Protein-1; PCL, poly(ϵ -caprolactone); AV-shunt, arteriovenous shunt; FBR, foreign body response; HA, hyaluronic acid; TGF- β_3 , Transforming Growth Factor- β_3 ; ECM, extracellular matrix; IFN- γ , Interferon- γ ; IL-4, Interleukin-4; NO2-OA, nitro-oleic acid.

hybrid scaffolds). However, common requirement is that the scaffolds are off-the-shelf available, avoiding many of the logistical and translational challenges pertaining to *in vitro* TE approaches.

Immunology plays a central role in this redefined vision on TE. This is not surprising given that tissue regeneration is inherently intertwined with the immune system [19–22]. The convergence of tissue engineering and immunoengineering has gained much attention over the past years, which is, for example, reflected by a recent Focus Edition on “Strategic Directions in Immunoresponsive Biomaterials in Tissue Engineering” in *Tissue Engineering Part A* [23], and the recent launch of dedicated scientific journals (e.g. *npj Regenerative Medicine*, *Journal of Immunology and Regenerative Medicine*). Nowadays, much research is devoted on the various ways to locally modulate the immune response, and primarily macrophages, via the scaffold design parameters (e.g. microstructure, material composition, inclusion of cytokines) with the aim to induce functional tissue regeneration. However, a true fundamental understanding is still lacking. Another important consideration lies in the notion that, even without considering any scaffold parameters, *in situ* TE is completely dependent on the natural regenerative potential of the scaffold recipient (Figure 1). The intrinsic regenerative capacity is highly variable between patients, and even between healthy individuals. There is a strong natural variability in both the innate and adaptive immune response among humans, which, to a large extent, can be attributed to differences in age or gender [24,25]. Consequently, young adults and fertile women are known to have an increased risk of scarring compared to men and elderly, which is attributable to variations in

the immune system [26,27]. Moreover, recipients from prostheses (e.g. heart valve replacements, blood vessel grafts) often suffer from systemic comorbidities, such as diabetes and chronic kidney failure, further contributing to the variability of the regenerative capacity and thereby, the applicability of such techniques for specific patient cohorts.

In this concise review we address the recent developments that are propelling the field of *in situ* TE and material-driven immunomodulatory strategies for regenerative medicine. Specifically, we will describe the pivotal role of the host response and highlight some of the most important recent findings in the rational design of immunomodulatory scaffolds to induce endogenous tissue regeneration. With the increasing number of studies demonstrating the Proof-of-principle of *in situ* TE and the concept of immunomodulation, the main challenge now lies in taking the step towards safe and robust clinical translation. Being inherently dependent on the host response, large inter-patient variability is to be anticipated in the efficacy of *in situ* TE treatments. Therefore, we will address the influence of scaffold-independent patient characteristics, as well as the evolution of enhanced predictive models (*in vitro*, *ex vivo*, *in silico*, *in vivo*), which are instrumental to the development of new, personalized immunoengineering strategies for regenerative medicine.

***In situ* tissue engineering and the foreign body response**

In situ TE relies on the endogenous regenerative capacity of the patient. Over time, newly formed tissue should gradually take over the function of the resorbing scaffold [28,29]. Therein, the main challenge lies in

Figure 1

The host response to an implanted biomaterial is dependent on various material-dependent parameters (A), as well as material-independent patient-specific characteristics (B); the latter warranting the need for personalized treatments.

inducing regeneration of functional tissue, rather than fibrotic scar tissue. In the case of normal wound healing, inflammatory processes direct the type of healing towards fibrosis or regeneration. For *in situ* TE, the inflammatory reaction is for a large part dependent on the implanted scaffold, which typically leads to a foreign body response (FBR). Crucial in that is that the host response to any implanted biomaterial is a continuum of reactions, as expertly reviewed in detail elsewhere [30,31] (Figure 2). Consequently, the final - ideally homeostatic-state of the newly formed tissue is dependent on the initial inflammatory response to the material. This opens the door for immunomodulatory strategies, as the initial inflammatory response, and thus tissue outcome, can be modulated via scaffold design parameters, with or without complementary systemic treatments. Importantly however, the severity and extent of the induced FBR is dependent on various patient characteristics.

Independent of the material composition or scaffold microstructural properties, the iatrogenic injury suffered from the implantation procedure causes the onset of inflammation. This is characterized by vasodilation of capillaries and release of cytokines and damage-associated molecular patterns (DAMPs) from activated platelets and injured cells, as well as damaged matrix components [31,32]. The onset of inflammation is dependent on various parameters unrelated to the scaffold, such as anatomical location, patient characteristics and the surgical procedure. In parallel to these

biomaterial-independent events, blood and serum proteins instantaneously adsorb to the material surface. The type and amount of adsorbing proteins is highly dynamic, and dependent on various material characteristics (e.g. topology, hydrophilicity). The adsorbed proteins form a provisional matrix, consisting of coagulation factors, complement factors (opsonins) and released DAMPs. The provisional matrix forms an interface between the foreign material and the host, with which the immune cells interact [32]. Proteins within the provisional matrix are recognized by pattern recognition receptors (PRRs) on innate immune cells (e.g. neutrophils and macrophages), marking the material for phagocytosis.

Neutrophils are typically the first cellular responders upon injury, marking the acute inflammatory phase [33]. Neutrophils are recruited via extravasation and chemotaxis towards chemoattractants (such as DAMPs), released by activated platelets and endothelial, as well as other damaged tissue-resident cells. Recruited neutrophils are typically short-lived 'kamikaze' cells, releasing chemicals, such as reactive oxygen species (ROS), proteases and chemokines, aimed to respectively break down the foreign material and to attract a secondary wave of neutrophils (mainly via interleukin-8; IL-8), as well as monocytes (e.g. via monocyte chemoattractant protein-1; MCP-1) to the scene. Within approximately 3–7 days after implantation, the acute inflammatory phase transitions into a chronic inflammatory response and – in case of scaffold presence-the

Figure 2

The host response to an implanted biomaterial is a cascade of events as depicted schematically (A) and apparent from recent *in vivo* data using a resorbable electrospun scaffold as an arterial replacement in the rat aorta (B–G). The cascade is ignited by the acute inflammatory response during the first 1–7 days after implantation, characterized by the infiltration of neutrophils and macrophages (CD68⁺, C), followed by a proliferative phase in which myofibroblasts are activated (α -SMA⁺, D) and new matrix is deposited via cross-talk with macrophages. The newly formed matrix is remodeled into a well-organized, functional tissue, here in the form of a well-organized neointima with α -SMA expression (E, F) and circumferentially aligned collagen (G, H; picrosirius red staining visualized with polarized light microscopy). Upon complete scaffold degradation, the goal is to achieve a physiological state of mechanical and biological tissue homeostasis. Scale bars represent 20 μ m (B, C), 50 μ m (D), 500 μ m (E, G), 200 μ m (F, H). Panel (A) adapted from Ref. [28], panels (B–D) reprinted and adapted, with permission, from TISSUE ENGINEERING, Part A, 2015, ten.tea.2015.0066, by Talacua et al. [2], published by Mary Ann Liebert, Inc., New Rochelle, NY.

FBR. Chronic inflammation is typically governed by macrophages and lymphocytes in the context of toxicity and infection [32]. In the context of scaffolds, chronic inflammation is typically associated with the FBR, governed by macrophages and foreign body giant cells (FBGCs). Regarding the latter, the role of lymphocytes in the (essentially non-immunogenic) FBR is largely unknown. However, lymphocytes are transiently observed during the FBR, interacting with macrophages and FBGCs in a juxtacrine and paracrine fashion, rather than having direct interactions with the biomaterial, as described in a series of studies by the group of Chang et al. [34].

During chronic inflammation and the FBR, macrophages govern breakdown of the foreign material, as well as

coordinate the formation of new tissue and/or a fibrous capsule via cross-talk to (myo)fibroblasts [35,36]. As is now well-established, macrophages can facilitate such a variety of processes by adapting their phenotype to various polarization states, instigated by local biochemical cues from, among others, T cells [37]. In a recent study, Dondossola et al. described the temporal development of a fibrous capsule around a synthetic implant using intravital imaging in the skin of mice. The authors demonstrate a crucial role for pro-inflammatory M1 macrophages and Vascular Endothelial Growth Factor (VEGF)-driven vascularization for the development of a fibrous capsule, with an inhibition of fibrotic encapsulation by macrophage and/or VEGF depletion [38]. In contrast, a recent study by Bank et al. describes the enhanced tissue capsule formation during the FBR in a

transgenic mouse model of macrophage depletion. Surprisingly, this study suggests that macrophages are required for generating a pro-inflammatory environment, but not for tissue capsule formation around an implanted biomaterial, despite a decrease in fibroblast-like cells as a result of macrophage depletion [39]. Irrespective of these discrepancies in cellular contributions, the thickness and organization of a fibrous capsule is dependent on the properties of the scaffold (e.g. porosity, degradation rate, surface roughness, surface chemistry). This notion can be exploited to engineer endogenous tissues by explicitly employing the FBR, for example in the application of TE vascular prostheses (reviewed by Geelhoed et al. [40]).

Immunomodulatory scaffolds for *in situ* tissue engineering

The bulk of *in situ* TE studies are aimed at locally modulating the inflammation-driven regeneration using the scaffold properties. Clearly, the material composition (e.g. synthetic, natural or hybrid) has a profound influence on the host response to a scaffold. In particular, natural matrices have the advantage of intrinsically carrying natural ligands and binding sites for cellular interactions, as well as allowing direct remodeling by the host cells. On the other hand, purely natural matrices offer limited control over various properties, such as mechanical properties and degradation rate, especially when using decellularized native tissues. Moreover, such scaffolds require donor tissue, which is prone to natural variability. For example, Sicari et al. revealed a striking effect of the age of the source animal on the regeneration of abdominal muscle tissue in rats using decellularized porcine small intestine submucosa (SIS) xenografts [41]. Synthetic-natural hybrid scaffolds can overcome many of these limitations by offering a greater level of control, while benefiting from the presence of natural components. The relevance of this is reflected by several studies reporting superior regenerative performance of synthetic-natural hybrid scaffolds in comparison with their purely synthetic counterparts [42,7,43].

Despite lacking intrinsic beneficial signaling molecules, synthetic scaffolds offer great potential for *in situ* TE as well, as their immunomodulatory properties can be tailored via many scaffold design parameters. These properties include for example the scaffold mechanical properties, microstructure, surface chemistry, topology, and degradation kinetics, as recently reviewed in more detail elsewhere [28,44,45]. These can be further boosted or tuned down by incorporating bioactive molecules, such as defined extracellular matrix (ECM) components, on-the-fly preseeded stem cells, or signaling factors (e.g. cytokines, growth factors, peptides).

Among the most important parameters of a synthetic scaffold for *in situ* TE are its degradation kinetics.

Permanent, non-degradable implants typically get stably encapsulated after long periods of implantation, due to the persistent FBR. Depending on the application, this may or may not hamper implant function in the long run. For example, fibrous encapsulation of complete artificial joints can help stabilize and fixate such prosthetics. However, since the goal of *in situ* TE is to replace damaged tissue with fully autologous living tissue, resorption of the original scaffold material is a prerequisite for this approach. More specifically, the challenge there lies in achieving a balance between scaffold degradation and tissue formation, ensuring maintained graft functionality at all times. Clearly, an appropriate degradation rate is dependent on the application and even the patient's intrinsic fibrogenic capacity. In general, extended presence of the synthetic material can lead to prolonged presence of phagocytes and FBGCs, leading to excessive fibrous encapsulation and fibrosis. Sanders et al. recently demonstrated that the presence of synthetic scaffold remnants in decellularized *in vitro* engineered constructs led to a significant increase in cell infiltration of granulocytes (i.e. neutrophils) [46], indicating that incomplete resorption may lead to persistent activation of the immune system. Another example is given in a study by De Valence et al., demonstrating fibrotic tissue formation and calcification in *in situ* TE blood vessels using slow-degrading polycaprolactone (PCL) [47]. Apart from the mere time of implantation, it is important to realize that scaffold degradation is dependent on the presence of cells and the type of cells. This is illustrated by recent findings by our group using synthetic heart valve scaffolds, demonstrating highly localized scaffold degradation in regions with a high degree of FBGC presence and rich in newly formed collagen [5]. Hence, apart from degradation rate, the mode of degradation (e.g. oxidative versus enzymatic) is an important design parameter to control the transient changes in mechanical properties and structural integrity of synthetic scaffolds [48]. Furthermore, by-products of degrading synthetic scaffolds can lead to enhanced inflammation. In this context, Washington et al. recently demonstrated that the formation of acidic by-products of degrading poly(lactic-co-glycolic acid) (PLGA) microparticles could be tuned by adapting the PLGA monomer sequence, and thereby strongly modulating the host response to these microparticles, for example in terms of FBGC presence [49].

Targeting macrophages within the immunological spectrum

Of all immune cells, macrophages are by far the most studied cells for immunomodulatory strategies for *in situ* TE. This is inspired by the now well-established commanding role of macrophages during wound healing, regulating the formation of new tissue in close cross-talk with myofibroblasts [35,36]. Concurrently, numerous

studies in regenerative species, such as axolotls and zebrafish, have proven that the innate immune system, and macrophages specifically, are absolutely essential for tissue regeneration [19–21]. Using a zebrafish model, Li et al. demonstrated that macrophages are essential for proper tissue regeneration and the resolution of inflammation, while neutrophils were dispensable for regeneration, despite being the primary phagocytes in response to injury [22]. A recent study by Godwin et al. revealed that the presence of macrophages was critical for the prevention of fibrosis during cardiac regeneration in axolotls [50]. Similarly, Simkin et al. demonstrated an essential role for macrophages and macrophage-produced ROS for tissue regeneration in African spiny mice. Therein, macrophage polarization was pinpointed as a distinguishing factor between regeneration and scarring, as illustrated by a specific spatial distribution of CD206⁺ M2 macrophages and a lack of CD86⁺ M1 macrophages during regeneration [51]. Translating this to *in situ* TE, systemic depletion of macrophages was shown to lead to a complete lack of regeneration of blood vessels and nerves in rodent models [52,11].

All these studies warrant the marking of macrophages as a primary target for *in situ* TE strategies. Nevertheless, it should be noted that the immune system acts as an intricate systemic mechanism, in which each cell type is playing its unique role, rather than being a collection of individual cell types. Therefore, strategies targeting other immune cells or the immune system as a whole can be equally effective, as targeting macrophages. For example, while the role of neutrophils in the biomaterial integration and regeneration is largely underexposed, recent work by the group of Bowlin et al. proposes a much more central role for neutrophils in those processes, priming the implanted biomaterial via the release of chemicals and neutrophil extracellular traps (NETs) [53]. NETs are fibrillary networks composed of the chromatin, which neutrophils can excrete upon activation by cytokines or microbes and their products, in order to trap pathogens and localize antimicrobial agents [53]. Interestingly, it was demonstrated that both the architecture (i.e. fiber diameter, pore size) and the material composition of electrospun scaffolds (synthetic versus natural versus hybrid) dictated the extent of neutrophil “NETosis” (release and activation of NETs) and downstream fibrous capsule formation in response to the scaffold [54]. In addition to innate immune cells (macrophages and neutrophils), recent studies are illuminating the role of the adaptive immune cells (e.g. T cells) in for *in situ* TE, as reviewed in more detail by Chung et al. [55]. Specifically, it was shown that scaffold-driven regeneration of traumatic muscle wounds is dependent on IL-4 signaling from T_H 2 cells [15], and that CD3⁺ T cells are involved in the signaling to CD206⁺ M2-like scaffold-associated macrophages in muscle injury in mice [16].

Host factors, translational models and personalized treatment

While most of the current *in situ* TE research is aimed at optimizing scaffold composition and design to trigger a favorable regenerative response, it should be noted that the host response to such a scaffold is strongly influenced by various patient-specific factors (e.g. age, gender, comorbidities, medication), as well as the anatomical location of the implant and the implantation procedure [32]. For example, the anatomical location determines the composition of resident cell populations that may or may not contribute to the regenerative process. Other highly relevant factors include blood contact, which may require additional modifications of the scaffold [56], and the biomechanical environment in which the scaffold functions. With respect to the latter, mechanical stimuli have been long known to have a determining effect on ECM remodeling. However, accumulating data indicate that also immune cells, and specifically macrophages, are mechanosensitive and can adapt their phenotype in response to mechanical stimuli (i.e. cyclic strains) in order to steer tissue formation and remodeling in cross-talk with secondary cells [57–60]. Moreover, we recently demonstrated that the colonization of electrospun meshes by specific human monocyte subsets *in vitro* is dependent on shear stresses [61], using a mesofluidics model of the circulatory system [62].

Apart from anatomical location, patient-specific factors have a profound influence on their immune system and regenerative capacity [25,63]. For example, aging strongly influences the redox balance and induces immunosenescence [32,64]. Consequently, the ability to form new tissue, but also the risk of fibrosis is reduced in the elderly, when compared to young patients. A recent study by Hachim et al. revealed a diminished macrophage response and an increase in the M1/M2 ratio following subcutaneous implantation of polypropylene meshes in old versus young mice (18 versus 8 weeks, respectively) [65]. Similar considerations have to be made for common comorbidities, such as obesity or diabetes. Studies by Socarrás et al. and Wang et al. demonstrate a distorted inflammatory profile and reduced fibrogenic capacity in response to implantation of synthetic meshes in diabetic rats, either subcutaneously or as aortic replacement graft, respectively [66,67]. These findings call for tailored strategies, capable of boosting or inhibiting certain regenerative events dependent on patient characteristics (Figure 3). One such example was recently reported by Kim et al., who demonstrated enhanced regeneration of critical-sized skin wounds in rats with induced type 1 diabetes by loading hydrogels with substance P [18].

All in all, relatively little information is available on the effects of patient characteristics on the endogenous regenerative capacity. However, material-testing models

Figure 3

Potential opportunities for personalized *in situ* tissue engineering strategies include (I) the systemic administration of complementary inflammatory mediators to either boost or inhibit inflammation, (II) the development of bioinstructive or bioresponsive materials, which can locally modulate the immune response and/or interact with local biological cues, and (III) the tailoring of scaffold degradation kinetics depending on the endogenous fibrogenic capacity of the patient, in order to maintain the balance between scaffold degradation and neotissue formation.

on all levels (i.e. *in vitro* [57,62,68]; *ex vivo* [69], *in silico* [70,71], *in vivo* [67,72]) are becoming increasingly refined in order to be predictive of the clinical situation. In addition to diseased animal models as previously mentioned, humanized *in vivo* models, such as recently described by Wang et al. [72], can be relevant models to partly circumvent inter-species differences in the immune response and the regenerative cascade. Human *in vitro* models are being developed to elucidate the effects of comorbidities on *in situ* TE treatments. Several *in vitro* models have been described based on human macrophages, with or without lipopolysaccharides-mediated stimulation, to predict the *in vivo* response towards synthetic scaffolds [68,73,74]. Therein, macrophage polarization state and cytokine secretion profiles are regarded as predictive readout parameters for long term tissue outcome, as previously proposed by Badylak et al. for natural matrices [75,76]. In that respect, Jannasch et al. underlined the importance of culture conditions on the predictive value of macrophage-based *in vitro* models [77], and Wolf et al. showed that the predictive value of protein secretion is improved by combining it with principal component analysis *in silico* [71]. Considering diseased patients, Boersema et al. investigated the response of macrophages isolated from obese patients to various biomaterials *in vitro*, demonstrating that the macrophage-secreted cytokine profile correlates to body mass index, with a more pro-inflammatory profile for obese patients [78]. Another highly relevant finding by the same group is that the effect of various common medications (i.e. rapamycin, dexamethasone, celecoxib,

pravastatin) on the biomaterial-induced macrophage response is material-dependent [79]. Increased levels of complexity in *in vitro* models can be achieved by co-culturing macrophages with fibroblasts or mesenchymal stem cells, either statically [80–83], or dynamically to account for the biomechanical environment [57,59]. Such models allow for a more direct investigation of the tissue forming properties of a scaffold, rather than relying purely on macrophage behavior.

Conclusion and future perspective

Taken together, increasing data is demonstrating the potential of *in situ* TE strategies using immunomodulatory scaffolds for a wide range of applications. However, the fundamental processes underlying immune-driven tissue regeneration remain largely unknown. Sophisticated models are being developed to unravel these mechanisms, but we have only scratched the surface of the true potential of these models. Therein, the patient and patient-specific characteristics should be the central pillar, in order to develop robust or even personalized clinical *in situ* TE therapies.

Acknowledgements

We acknowledge Dr. Leda Klouda for critical review of the manuscript. This work was supported by the BMM iValve and iValve-II projects, co-funded by the Dutch Ministry of Economic Affairs and the Netherlands Heart Foundation. A.S. received funding from the Netherlands Cardio Vascular Research Initiative: the Netherlands Heart Foundation, Dutch Federation of University Medical Centers, the Netherlands Organization for Health Research and Development and the Royal Netherlands Academy of Arts and Sciences (CVON iValve). We also gratefully acknowledge funding for the Gravitation Program “Materials Driven Regeneration” by the Netherlands Organization for Scientific Research.

Conflict of interest

The authors declare no conflicts of interest.

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- of special interest
- of outstanding interest

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