npj | biomedical innovations

Review

https://doi.org/10.1038/s44385-025-00053-7

Don't judge an implant by its cover: how the foreign body response and fibrotic capsule might be harnessed for good

Mary E. Dickenson[1], Robert S. Oakes[2,3] & Aaron H. Morris[1,4] ✉

Biomaterials are widely used, yet when implanted, they elicit a complex reaction from the host called the foreign body response (FBR). Although the FBR is typically viewed as a deleterious response to implants, many potential benefits of the FBR have recently been identified. This review highlights the variety of ways that the FBR has been harnessed for positive outcomes, including tissue engineering and disease monitoring.

The foreign body response (FBR)

The FBR is an inflammatory response mounted as a reaction to foreign materials that are implanted within, or otherwise introduced to, the body. This response is characterized by an initial cascade of acute inflammation and leads to eventual fibrotic encapsulation of the foreign material[1–3]. The FBR and associated inflammatory and fibrotic responses result in failure of many implanted devices, prompting continued study of the FBR[4].

When a foreign material is implanted, it elicits a complicated response composed of both innate and adaptive immune cells (Fig. 1). In general, this response has historically been divided into a few primary stages: protein adsorption, acute inflammation, chronic inflammation, and fibrotic encapsulation[1,2,5]. We present a brief overview of inflammatory cascades that characterize the FBR response here. For more details, there are many recent reviews on the topic[1,5–8].

Protein adsorption

Whether introduced via injection or a surgical method, the implantation of a foreign material damages surrounding tissue, which subsequently activates an initial inflammatory response[2,5]. Within minutes of implantation, a layer of proteins adsorbs to the material surface, allowing for infiltrating cells to interact with the material. This protein-surface matrix is highly dynamic, undergoing protein adsorption-displacement classified by proteins of lower molecular weight arriving first and subsequently being replaced by proteins of higher molecular weight as time passes, yielding longitudinally dynamic protein compositions[1,2,5,9,10]. These surface-protein characteristics are not only influenced by time, but also by the type of foreign material being introduced, demonstrating one of the many ways that the FBR can vary with respect to the materials being implanted[11,12].

Acute inflammation

Protein adsorption paves the way for the cascade of cellular events that compose the FBR. Neutrophils migrate to the site of the foreign body within minutes of implantation, marking the beginning of the acute inflammatory phase. These neutrophils adhere to the provisional matrix formed by the adsorbed proteins on the surface of the material and release factors that contribute to the recruitment of additional immune cells, namely monocytes[1,9,13]. As monocytes arrive at the implant site, they begin to differentiate into macrophages that subsequently proliferate and adhere to the surface of the material. The macrophages bound to the surface of the implant then spread over the surface of the implant and attempt to engulf and phagocytose it[1]. In the case that the macrophages can successfully phagocytose the material in this acute phase, the FBR will resolve. However, many implanted materials are either too large or are not degradable, resulting in the transition to the chronic stage of the FBR[1,3,5,14].

Chronic inflammation and fibrotic encapsulation

Classically, the transition of the FBR from the acute phase to the chronic phase is thought to be characterized by the evolution from an explicitly inflammatory reaction into a fibrotic process. This transition into the chronic stage of the FBR occurs within the first few weeks post-implantation, and, unless the implant is either destroyed or removed by external processes, will continue indefinitely[5]. Key to this transition is the shift of macrophages from a pro-inflammatory (M1) phenotype to an anti-inflammatory (M2) phenotype that is associated with tissue regeneration, and in the case of foreign materials, the formation of a fibrotic capsule around the foreign body. We acknowledge that classifying macrophage polarization into pro- and anti-inflammatory states is an oversimplification of the biology, as these cells are likely polarized on a spectrum[15,16]. With that limitation in mind, we feel that this terminology is a helpful heuristic to

[1]Department of Biomedical Engineering, University of Michigan, Ann Arbor, MI, USA. [2]Department of Biomedical Engineering, University of Delaware, Newark, DE, USA. [3]Veterans Affairs Maryland Health Care System, United States Department of Veterans Affairs, Baltimore, MD, USA. [4]Cellular and Molecular Biology Program, University of Michigan, Ann Arbor, MI, USA. ✉e-mail: aharmorr@umich.edu

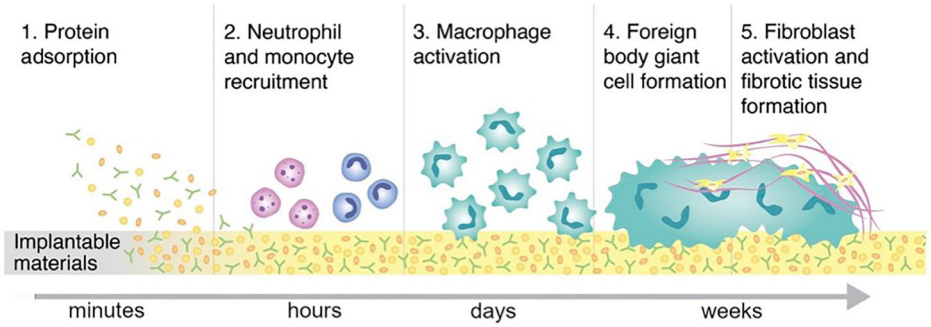

Fig. 1 | Schematic of the primary stages of the FBR and fibrotic capsule formation. This figure has been republished as permitted from an open-access article under the terms of the Creative Commons Attribution License[38].

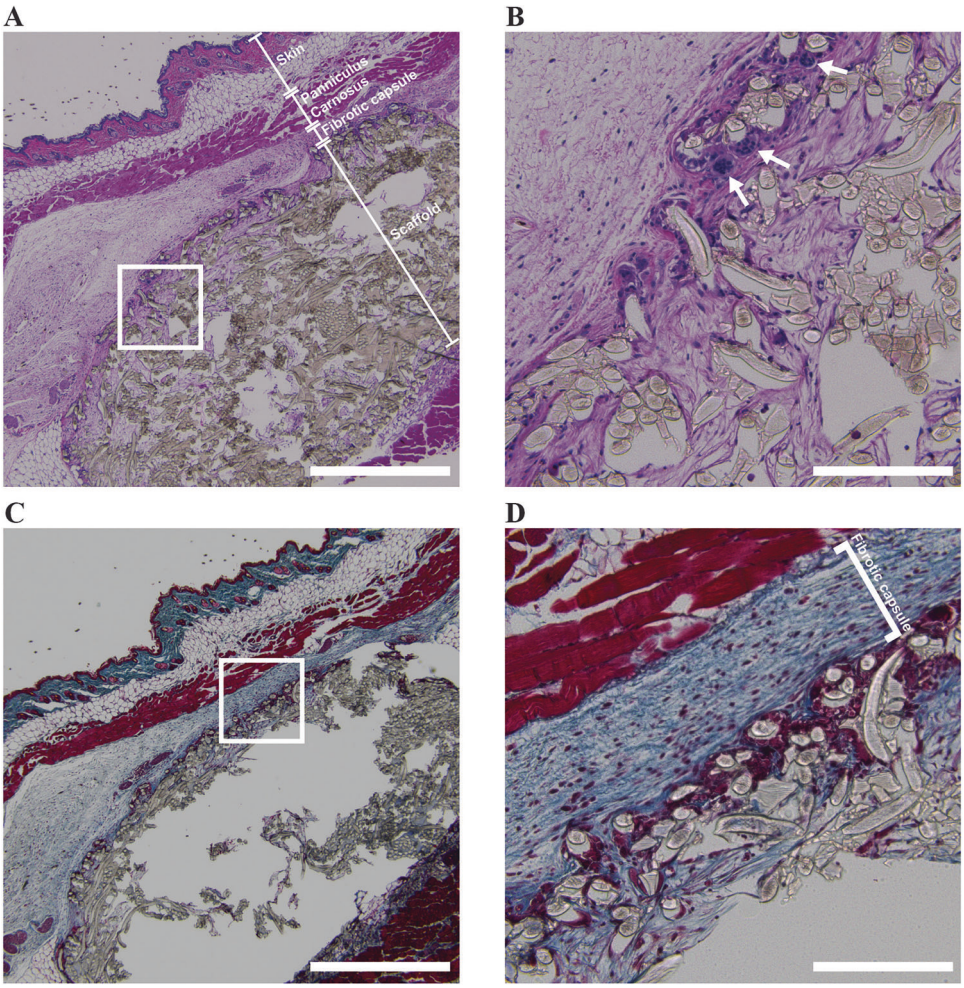

Fig. 2 | Histological images showing the FBR to Bard 3080 low porosity polytetrafluoroethylene felt 28 days post subcutaneous implantation in C57BL/6J mice. Hematoxylin and eosin representative image of explanted scaffold and resulting FBR at 4× (**A**) and 20× magnification (**B**), with arrows denoting examples of FBGCs. Masson's trichrome representative image of explanted scaffold and resulting FBR at 4× (**C**) and 20× magnification (**D**), with the fibrotic capsule denoted in D. Inset boxes in (**A**, **C**) denote the locations of the magnified images in subpanels (**B**, **D**). Scale bars are 1000 μm and 200 μm in images (**A**, **C**) and images (**B**, **D**), respectively.

discuss this topic and accurately reflect previously published results that have characterized macrophages in this manner. M2 macrophages become key players in the attraction and organization of fibroblasts to the surface of the foreign material[8,17–19]. These fibroblasts subsequently begin depositing extracellular matrix (ECM) around the foreign body[20]. Another unique hallmark of the FBR is the fusion of clusters of macrophages into polynucleate foreign body giant cells (FBGCs), which are capable of phagocytosing much larger materials than their macrophage counterparts[1,9]. These FBGCs are unique, displaying traits similar to both macrophages and osteoclasts[21], and they are more effective at damaging biomaterials than macrophages[22]. Over the course of days to weeks, this buildup of macrophages, FBGCs, fibroblasts, and secreted ECM culminates in the formation of a fibrotic capsule, thickening over the course of months to completely isolate the foreign material from the surrounding tissue[5] (Fig. 2).

This FBR capsule poses significant challenges to the longevity and function of implanted biomaterials. While the acute inflammatory stage of the FBR is characterized by a more direct immune attack on the implanted foreign materials, the fibrotic capsule creates a thick physical barrier between the implanted device and the surrounding tissue[1,5,23]. Additionally, the fibroblasts forming this fibrotic capsule will begin to contract around the material trapped within it, and this physical force can be detrimental to implants (for example, capsular contraction is a key failure mode of breast implants)[24]. Due to these challenges, fibrotic capsules have become one of the leading causes of chronic failure for implants[25–27].

The FBR differs in response to anatomical location and disease

Importantly, the FBR acts differently in different anatomical locations, as well as in the context of different diseases, age, and obesity[28–33]. For example,

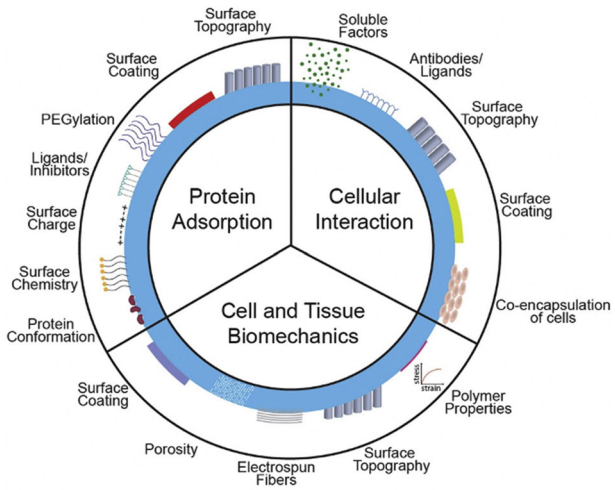

Fig. 3 | Graphical representation of three major types of strategies used to mitigate the FBR and fibrotic encapsulation: cellular interaction, cell and tissue biomechanics, and protein adsorption. Tailoring of these material characteristics can result in a minimized FBR post-implantation in vivo. This figure has been republished with permission[268].

it is known that the FBR in both the central nervous system (CNS) (distinctly including the formation of an astroglial border in the CNS[34,35]) and in the epicardium (demonstrating increased levels of implant degradation as compared to the subcutaneous space[36]) are unique from other areas of the body, which consequently affects biomaterial function. This review does not discuss the specific complexities of the FBR in the CNS or the field of neuroimplants, because many of the cellular responses in the CNS differ from those described here and there has not yet been substantial investigation into the upsides of the CNS FBR. With regards to disease states, researchers found that the FBR is altered in both inflamed and cancerous tissue due to neutrophil, macrophage, and FBGC infiltration being modified as a result of prior inflammation, and noted that further examination of the FBR in disease states can lead to more biologically informed material designs[37]. Together, this highlights not only the importance of considering natural responses such as the FBR when designing implantable healthcare devices, but also the intersection of disease state and implant-associated inflammation, which have unique, yet connected, immune responses that cumulatively affect how a material functions once implanted.

A historical view of the FBR and techniques used to mitigate it

Historically, biomedical scientists and healthcare professionals have looked upon the FBR exclusively as a negative response to implanted materials that needs to be mitigated. The negative opinion of the FBR stems from its presenting a challenge to the efficacy and lifespan of medical devices that need to be implanted for extended periods of time. Devices within this class have only become more common in recent years, and device failure due to the FBR costs $10 billion annually[6,38,39]. The FBR evolved to remove or encapsulate any foreign materials that are introduced which might otherwise cause harm, acting as a defense mechanism against unknown materials. This reaction can be extremely hard on implants, both in the acute phase with the secretion of degradative enzymes and reactive oxygen species, and in the chronic phase which leads to the fibrotic capsule around the implant[1,5].

Scientists have attempted to tune almost every aspect of implantable materials in an effort to mitigate the FBR (Fig. 3), leveraging the fact that different materials elicit inherently different FBRs. These alterations have ranged from modifications of material and surface chemistries, altering the material size and surface topography, and incorporating drugs or bioactive proteins. Due to the dynamic nature of the FBR, it is paramount to acknowledge that some of the approaches discussed here to minimize the FBR might work well in the acute phase but not in the chronic phase. While none of these techniques has been able to fully elude the FBR, there has been progress toward minimizing the negative impacts of the FBR so various implants and devices can now function for much longer than was possible a few decades ago[4,6,38–40].

Material chemistry

The chemical composition of an implant alters the immune response to the material, and thus scientists have attempted to alter material chemistry to manage the FBR[4,13,41,42]. Naturally-derived ECM-based biomaterials have been widely explored[42], and these materials inherently elicit a lessened FBR than that seen in response to synthetic materials[43–45]. It has been shown that the surface chemistry of materials (hydrophobic, hydrophilic, anionic, or cationic) impacts cellular interactions with surfaces, and consequently, affects the FBR[46,47]. Various materials have also been fabricated to resist protein adsorption, such as zwitterionic and polypeptide materials. Zwitterionic materials, the class of which includes carboxybetaine, sulfobetaine, and phosphorylcholine chemistries, are classified by having equal numbers of anionic and cationic groups, which causes this class of materials to be highly hydrophilic and antifouling[39,41]. Due to their natural antifouling properties, these materials have been used to develop implants that elicit very mild FBR[48–51]. Similarly, polypeptide materials with antifouling properties have recently gained traction for use in implanted devices as they exhibit a reduced FBR[39,52–54]. Given that different material chemistries and surface chemistries yield vastly different material properties, these studies cannot inform a one-material-fits-all type of conclusion, but instead should be used to make informed decisions about which materials might be the most appropriate for different use cases based on the desired properties and outcomes of the material.

Physical material characteristics

The surface topography, geometry, and size of an implant play a key role in the FBR, particularly the alteration of surface features on a micron-scale[55–58], the geometrical smoothness of the implant[59–61], and the overall size of the material[61,62]. Surface topography regulates the proteins adsorbed to the surface, with some topographies leading to reduced adsorbed protein densities and consequently less pro-inflammatory cell activities. A clinical trial investigating the fibrotic capsule formation around breast implants with two different surface topographies found that implants with a reduced surface roughness yielded lower levels of capsule formation (NCT05648929)[63]. Of note, work has also been done to modify the surface topography of implanted materials with the goal of achieving a more natural tissue capsule, moving towards modulating the FBR towards a more desirable outcome rather than wholly eliminating it[55]. Similar to textured materials, porous implants have demonstrated less aggressive FBR as compared to non-porous materials with vast potential utility in tissue reconstruction[64,65], though the exact details of this phenomenon remain unclear[66,67]. In addition to surface topography, the overall shape and size of materials have been observed to play a pivotal role in the magnitude of the FBR. Studies have indicated that smooth material geometries without acute angles inherently minimize the FBR to implants[59,60], and that a large spherical shape (having a diameter of 1.5 mm or greater) might be the optimal geometry for minimizing host fibrosis[61]. These techniques show promise in yielding minimized fibrotic capsule formation around implants due to altered protein adsorption, lower levels of pro-inflammatory cues, and lessened cell adhesion and proliferation.

Delivery of bioactive drugs or biomolecules

It is clear that modulation of the FBR with systemic delivery of pharmaceuticals is possible[68], but more precisely controlled delivery of anti-inflammatory drugs at the site of the implant to locally control cell populations and activities shows promise in mitigating off-target effects[6,69,70]. Corticosteroids have been loaded into implantable biomaterials to help mediate both acute and chronic inflammation at the site of the implant[71,72].

Within this space, there are multiple ongoing clinical trials assessing the safety and efficacy of dexamethasone-eluting cochlear implants to help reduce inflammation and the FBR (NCT06142682 and NCT06424262)[73]. Of note, the use of steroids to control the FBR is suspected to have downsides, including decreased angiogenesis[74], though there are conflicting reports in this space showing opposing findings[75]. Extensive work has investigated delivering a variety of drug types (e.g., immunosuppressants/anti-inflammatory drugs[71,74,76], cytokines[77,78], or small-interfering RNA[79,80]) in a number of different ways (e.g., drug coatings[76,81] or encapsulation[71]), and this body of work continues to be studied and expanded upon[6,39,41]. Interleukin-4 (IL-4) eluting implants promote macrophage polarization at the site of the implant towards an M2-like, anti-inflammatory phenotype[82]. Similarly, hydrogels with interleukin-33 conjugated to their surface stimulate macrophages on the implant surface to upregulate a type 2-like immune response[83]. Each of these phenotypical changes promoted by cytokines integrated into implanted materials led to lessened inflammatory responses and improved implant integration.

Mechanical actuation of implants

Signaling via mechanoreceptors and mechanical mismatch between implants and their surrounding tissue appear to have an important role in the FBR[84,85]. Leveraging this, the inclusion of mechanical actuation within implanted materials has been used as a method to modulate the FBR. To demonstrate this, biomaterials were implanted subcutaneously in both rats and mice and were then intermittently subjected to mechanical pressure[84,86]. Over the course of 2 weeks, the mechanical actuation was found to significantly reduce the fibrotic capsule thickness and myofibroblast presence around the site of the implant in both animal models, as compared to non-actuated controls. Conversely, it has been shown that implants vibrating at a significantly higher frequency (200 Hz as compared to 1 Hz used in the previously described studies) generate a more severe FBR[87], demonstrating the ability of these exerted mechanical forces to modulate the FBR.

Animal models for the study of the FBR

To continue to study and optimize materials for the complexities of the FBR, accurate models are required. Two animal models commonly used to study the FBR are rodents and non-human primates. Rodents have some anatomical and genetic similarities to humans[88], but they do not accurately recapitulate the timescale and severity of the FBR experienced in humans[87]. Despite this, these animal models have been used as helpful platforms for screening materials and potential therapeutic targets that might help minimize the FBR[89,90]. Interestingly, incorporation of mechanical vibrations has been shown to create a more human-like FBR in C57BL/6 mice, which is the most widely used mouse model[87]. This result is thought to be at least partially attributed to the allometric scaling of forces, where the mechanical stresses experienced by tissues increase exponentially with respect to increases in body size. Of note, different strains of mice exhibit inherently different FBRs to the same implanted materials[91], urging the careful selection of animal models. Humanized mouse models have emerged as a way to create a more human-like FBR, enabling the further study of these important immune interactions[92,93].

Clearly, the wealth of literature surrounding methods for attenuating the FBR suggests that by manipulating material properties, we can engineer aspects of the FBR. These studies will provide insights into many different control mechanisms as we move our focus towards leveraging the FBR for positive outcomes. For further information, see the many excellent review articles that discuss studying and attenuating the FBR[4,6,38–40,94,95].

Moving toward the future: shedding a positive light on the FBR

Although the FBR has historically been viewed as a negative response that needs to be ameliorated, an array of new immunoengineering and tissue engineering techniques has reframed the FBR as something that can instead be leveraged for a useful outcome[96–98]. The first clear attempt to harness the FBR was in the 1960s, when Charles Sparks leveraged the FBR to rods implanted in the body to grow a fibrotic tube of tissue in situ to be used as an autologous vascular graft[99]. Since then, our knowledge of the FBR has expanded tremendously, and consequently so have the potential applications for harnessing it. More recently, the possible outcomes of the FBR have been applied to many different tissue engineering applications[14], as a way to recruit cells to a predetermined scaffold site for disease diagnosis or treatment[100], and even as a method for increasing vaccine efficacy[101] (Fig. 4). This review will discuss the ways in which the FBR has been leveraged as a tool and provide an outlook into how bioengineers can continue to harness this response in new and innovative applications moving forward.

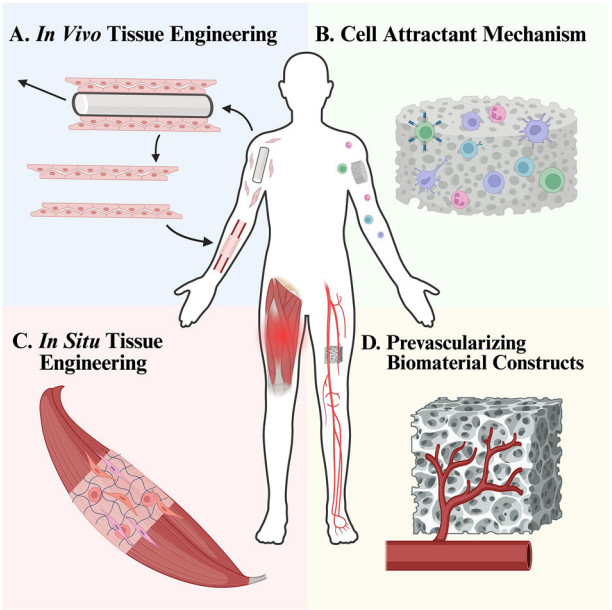

Fig. 4 | Different techniques and applications that have benefited from leveraging the FBR. A Leveraging byproducts of the FBR, such as fibrotic capsules, for applications in in vivo tissue engineering. **B** Using the FBR as a method to improve tissue formation and integration within engineered material constructs. **C** Harnessing the FBR as a cell attractant mechanism to a predetermined site for the improvement of disease diagnosis and treatment and for increasing vaccine efficacy. **D** Utilizing the FBR as a method to aid in the prevascularization of biomaterial constructs. Figure was generated in BioRender.

Harnessing the FBR for in vivo tissue engineering

Over the last 80 years, various aspects of the FBR have been harnessed to engineer tissue, from the fibrotic capsule it forms, to the tissue remodeling it can elicit, to the large recruitment of cells it causes to the site of an implant. The earliest applications of harnessing the FBR for a positive outcome were within the in vivo tissue engineering field. This section will discuss applications that have specifically used the FBR to form a fibrotic capsule around an implant with the goal of later removing the implant and using the remaining capsular tissue.

Autogenous vascular grafts

Immune responses to implanted biomaterials and transplanted tissues have been a longstanding challenge in medicine[102,103], thus necessitating the use of autologous tissue for many applications to avoid this immune reaction[99]. Autologous tissue provides a source material that avoids rejection, but poses other challenges including lack of available tissue, damage to sites of tissue harvesting, and inadequate function of native tissues. To meet this need, researchers noted that fibrotic capsules form around implanted materials within a relatively short period of time, and that these fibrotic capsules could then be used as autologous grafts without having to take functional tissues from other areas[99,104]. This technique of harnessing the FBR to implanted materials has specifically been used to develop autogenous vascular grafts.

Scientists implanted rods within the subcutaneous space or thoracic cavity to generate tissue capsules for use as autologous vascular grafts, or hemodialysis ports, primarily in patients who do not have saphenous veins available for use. Sparks and his colleagues were responsible for much of the early work within this area, developing a tissue die consisting of an outer tubular shell and an inner mandril, with a knitted Dacron tube loaded between these two layers to help reinforce the fibrotic capsule that was expected to form. This allowed for the growth of a tubular fibrotic graft of prespecified dimensions to be grown with one's own cells, and then transplanted within a few weeks to the graft site with little to no observed immune response[99,105,106]. While these early autologous grafts had high rates of complications in patients (namely aneurysm formation and rupture)[107,108], this work pioneered the harnessing of the FBR to make autologous vascular grafts[109–112].

In more recent years, significant improvements have been made in engineering the FBR to achieve the desired tissue properties needed for these autologous vascular grafts to be successful. Briefly, Rothuizen et al. engineered polymer rods by altering the ratios of polymers used to fabricate these rods, as well as testing an array of surface modifications to elicit a controlled inflammatory response that yielded a fibrotic capsule of desired cell composition (dominated by myofibroblasts) and thickness (generally thicker capsules were considered superior due to their improved durability)[113]. These engineered co-polymer (poly(ethylene oxide terephthalate)–poly(butylene terephthalate)) rods were implanted subcutaneously in a porcine model to elicit a fibrocellular capsule with adequate mechanical strength and burst pressure, and were shown to differentiate towards a vascular phenotype after being integrated as autologous carotid artery interposition grafts[114]. Interestingly, Bezhaeva et al. also studied this technique within a chronic kidney disease model (the most common disease for hemodialysis patients), wherein they showed the importance of the macrophage-to-myofibroblast differentiation pathway and the contribution of both functional bone-marrow-derived and tissue-resident cells to the formation of a tissue capsule around foreign bodies[115]. Work in this area is ongoing, with investigations into the remodeling capacity of these tissue-engineered vascular grafts[116], the synthetic reinforcement of these grafts to improve mechanical characteristics[117], and further engineering of the implanted foreign materials to optimize the resultant autologous vascular grafts[118,119].

FBR-derived autogenous grafts have shown such promise that a group has worked towards the commercialization of these materials, having coined the term "Biotubes" for their silicone rod-based vascular graft system[120–123] (Fig. 5A-D). Notably, these Biotubes have shown success in the clinic, having performed well as an autologous vascular graft in a first clinical application in a pediatric patient for seven months post-implantation[124]. There is ongoing research to continue to improve the Biotube technology, specifically allowing for the creation of longer vascular grafts that can be used for below-knee bypass surgery[125–127]. Since then, additional first-in-human tests have yielded positive results in a distal bypass application for a patient with chronic ischemia of the leg[128,129], suggesting that this technology might soon become more widely adopted in the clinic.

For more details on the successes and failures of autologous vascular grafts, see recent reviews[130–134].

Fibrotic capsules for anchoring implanted materials

The FBR has also been leveraged to form a fibrotic capsule that can subsequently be used to hold grafted material in place. This type of approach is most commonly used for treating large bone defects and is referred to as the Masquelet, or induced membrane, technique. Briefly, polymethyl methacrylate cement spacers are placed into the bone defect area and are removed after several weeks once a fibrotic capsule has had time to form around the spacers. The spacers are then replaced with a bone graft, and the capsule from the FBR helps to hold the bone graft in place, prevents rapid resorption, and promotes vascularization of the graft[135] (Fig. 5E—F). While the fibrotic capsule generated from the FBR can yield a hypoxic environment due to its dense ECM composition, the Masquelet technique yields a highly vascularized membrane that secretes vascular endothelial growth factor at 2- and 4-week timepoints[136]. This discrepancy in anticipated vs clinically observed capsule vascularization might be partially attributed to the relatively early timepoints at which the cement spacers are removed, where vascular remodeling that might otherwise result in an avascular capsule has not yet occurred. This clinically used technique demonstrates the utility of leveraging the FBR to materials for a positive outcome[137]. As this is one of the preferred methods worldwide for critical bone defect reconstruction[138], there has been much work done to continue to advance this approach, and additional information on this technique and its associated advancements is available[136,137,139–150].

Similar in concept to the Masquelet technique is an approach to improving the transplantation survival of pancreatic islets by harnessing the FBR. The low survival of islet cells post-transplantation due to lack of vascularization and the invasive nature of alternative transplant procedures into the liver presents a large challenge for islet graft-mediated treatment of diabetes. To combat this, researchers have studied the use of the FBR to create a pre-vascularized, subcutaneous pocket that can act as a synthetic pancreatic environment for the improved survival, monitoring, and access to implanted islets. Briefly, a biomaterial scaffold was implanted subcutaneously, left in the subcutaneous space for long enough to form a vascularized fibrotic capsule around the material, and then the material was removed and islet cells were inserted in the fibrotic pocket that had formed. Multiple groups have shown preliminary results demonstrating increased islet survival and improved glycemic control in the groups using the FBR-pocket technique as compared to implantation into an unmodified subcutaneous space when tested in small animal models[151–153]. While fibrotic capsule formation is still considered a hurdle to delivering encapsulated cells, a clinical trial to test the safety and efficacy of leveraging a vascularized foreign body capsule to anchor islets is currently ongoing (NCT03513939)[154]. Of note, this technique has additionally shown preliminary success in the application of forming a prevascularized tissue space for the successful transplantation of hair follicle-associated cells and subsequent regeneration of hair[155], indicating that this technique might be relevant to other transplant applications.

The FBR has been harnessed in other applications for the improved integration or anchoring of medical devices. Whereas the FBR to implanted medical devices typically results in the surrounding of these implants with a dense, avascular capsule, work has been done to modify the surface of implants to drive a more favorable and tunable FBR. One study showed that depositing coatings on soft tissue implants to create tunable macro-scale pores on these surfaces allowed for the modulation of the FBR to these implants towards more favorable outcomes. They specifically noted that the dimensions of these macropores correlated with the degree of tissue integration, capsule characteristics, and angiogenesis around the implant[156]. Another group was aiming to improve methods for attaching a robotic cardiac compression sleeve to the external surface of the heart. They found that using a mesh-based sleeve allowed for the FBR to yield ingrowth of fibrous tissue into the pores of the material, thereby better integrating it with and anchoring it to the native cardiac tissue as compared to a non-porous material[157].

Leveraging the FBR to prevascularize acellular biomaterial constructs

Inadequate or non-functional vascularization of biomaterial constructs is a limiting factor in tissue engineering, because this leads to inadequate nutrient and oxygen supply to these areas[158]. An approach to ameliorate this issue is to harness the FBR to help bring cells to the site of the construct and allow them to infiltrate the material, which has been shown to lead to the prevascularization of these constructs[159]. Although the FBR is often viewed as a hindrance to functional vascular tissue in the peri-implant space due to inflammatory effects on vascular integrity and diffusion limitations imparted by the fibrotic capsule, with the right signals and approach, the FBR can be used to enhance aspects of biomaterial vascularization. In this section of the review, we will focus explicitly on acellular biomaterial

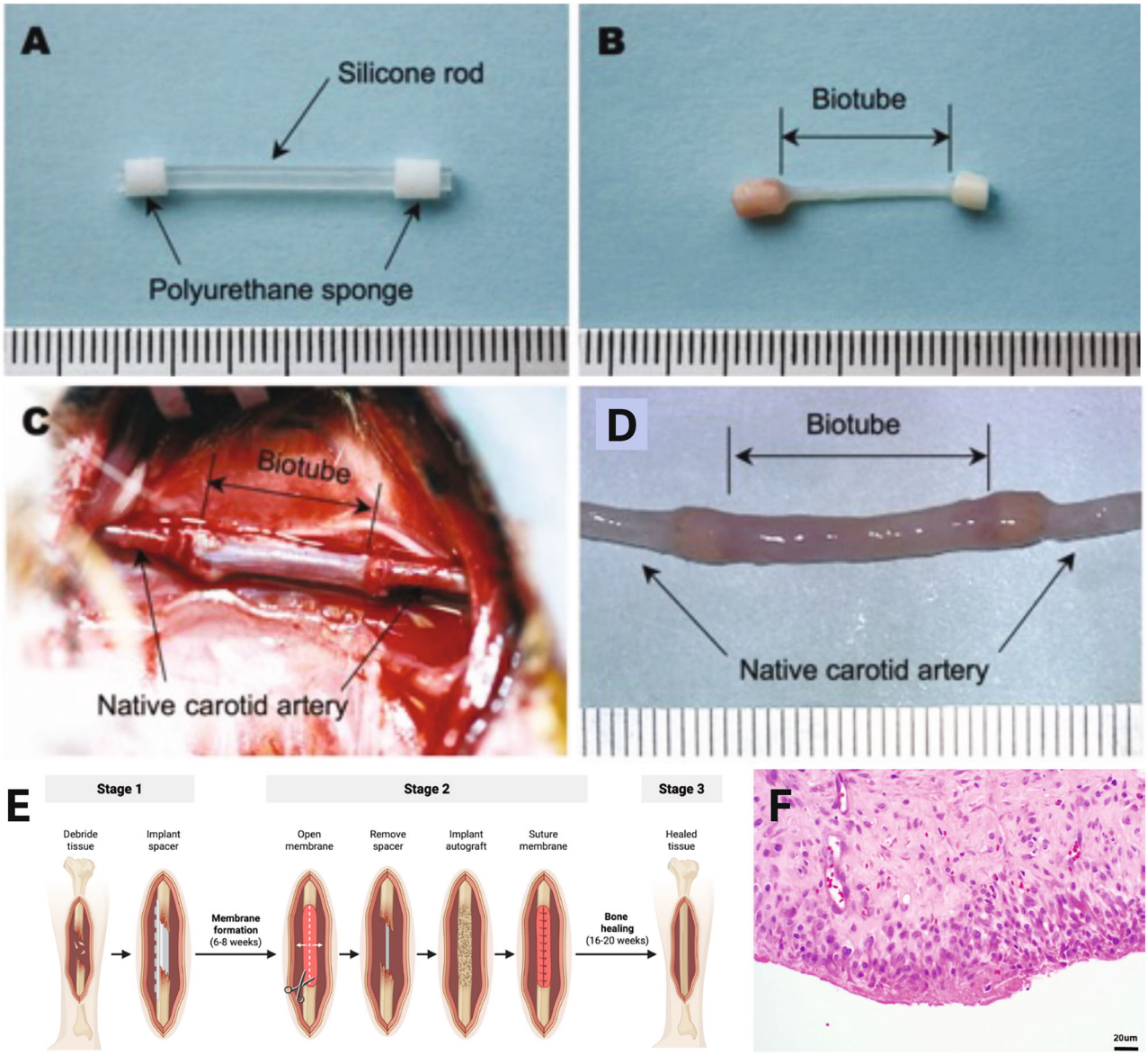

Fig. 5 | Leveraging the FBR for vascular and bone tissue engineering applications. Macroscopic photos showing the silicone rod-based implant (**A**) and the harvested Biotube 2 months post-implantation in the dorsal subcutaneous pouch of a rabbit (**B**). The Biotube was then implanted in a rabbit carotid artery (**C**) and harvested and imaged after 12 weeks (**D**). A schematic showing the process of the Masquelet technique (**E**). A Histology and Eosin (H&E) section of an induced membrane formed in response to implanted PMMA spacers in an ovine critical-sized bone defect model (**F**). All portions of this figure have either been republished with permission from the prior publisher[121], under the Creative Commons Attribution License[269], or from a modified Biorender template[270].

constructs and the associated FBR rather than the complex signaling cascades involved in the introduction of cellularized biomaterial constructs; however, there have been many studies applying these techniques to cell-containing materials. Three main techniques have gained traction to prevascularize acellular biomaterial constructs via the FBR: angiogenic ingrowth, the flap technique, and the AV loop technique[160–162].

Angiogenic ingrowth

The angiogenic ingrowth technique directly harnesses the FBR as a means for prevascularizing the construct in situ, using natural responses to create a sort of bioreactor environment[160] (Fig. 6A). A biomaterial scaffold is implanted (ideally in a location that is well vascularized and easily accessible, such as subcutaneously[163] or in a muscle pouch[164]), the FBR is elicited against this new material, and cells flood the area. This results in an angiogenic tissue response wherein microvessels begin to grow into the scaffold from the surrounding vasculature. After sufficient vascularization has formed within the scaffold, the material can be excised and transferred to the desired end location with little donor site tissue morbidity[165]. Notably, this technique does rely heavily on random inosculation between the preformed microvessels within the construct and the host vasculature at the transplant site, which does not occur immediately post-transplantation. Work has been done to accelerate this random interconnection of material and host microvessels, primarily using short-term in vitro culture of the prevascularized constructs prior to transplantation[166,167]. Despite these advances, this technique will likely never yield immediate perfusion of the scaffold microvasculature post-transplant, so alternative in situ vascularization techniques that allow for the immediate surgical anastomosis of the scaffold construct have gained more traction.

Flap technique

The flap technique is an extension of the angiogenic ingrowth technique, wherein a scaffold construct is implanted into a muscle flap to allow for the

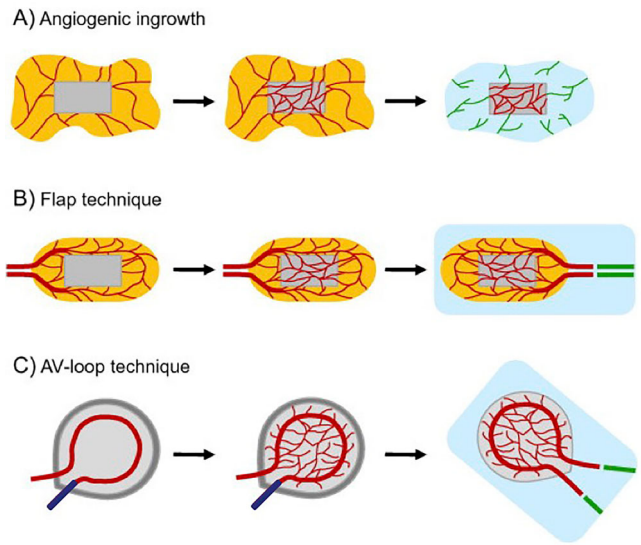

Fig. 6 | Schematic outlining the three in situ prevascularization approaches, which, in part, leverage the FBR to attract cells and encourage vasculature to form within an implanted scaffold material. These approaches are angiogenic ingrowth (**A**), the flap technique (**B**), and the AV-loop technique (**C**). Vasculature is represented in red (**A**, **B**). Veins are represented in dark blue and arteries are represented in red (**C**). Implanted materials are shown in gray, local tissue in orange, transplantation to the final defect site in light blue, and host vasculature at the final defect site in green (**A**–**C**). This figure has been adapted from a previously published figure with permission[160].

ingrowth of microvasculature from the surrounding muscle area into the biomaterial (Fig. 6B). Post-angiogenic ingrowth, the entire flap construct (muscle and embedded scaffold) is excised and transplanted to the site of the tissue defect where the major vasculature from the transplant can be surgically connected to the host vasculature at the implant site[164,168–171]. A major downside to this technique is that it causes significant tissue loss at the site of the muscle flap, but, conversely to the pure angiogenic ingrowth technique, it allows for immediate anastomosis and reperfusion of the scaffold post-transplantation. This technique saw its first successful clinical application in 2004 for the reconstruction of a large mandibular defect[172,173], but still requires further advancements for wide clinical adoption of this method.

AV-loop technique

In 1980, it was discovered that an arteriovenous (AV) fistula could be surgically formed by connecting an artery and a vein in the shape of a loop and that vasculature would spontaneously sprout out of this loop structure[174]. Using this knowledge, researchers found that material constructs placed within this AV-loop would become prevascularized[175] (Fig. 6C). While the prevascularization occurring from this technique cannot be attributed solely to the FBR, the FBR plays a role as it does in the other angiogenic ingrowth techniques discussed above, as evidenced by varied materials altering the degree of vascularity (described below). Interestingly, this method has been used to fabricate vascularized mature fibrous tissues using only a cylindrical plastic growth chamber to house the AV-loop (not requiring any additional scaffold material within the growth chamber), further suggesting the involvement of the FBR for the success of this technique[176]. This AV-loop approach has continued to be applied to the tissue engineering space because of its ability to form prevascularized scaffolds that can be transplanted and surgically anastomosed at the location of interest, as well as not leading to extensive morbidity at the donor site[158,161,177,178]. A variety of scaffold materials have been assessed using the AV-loop technique, demonstrating the impact of the type of material being implanted on the vascularization and tissue formation within the AV-loop[179–182]. One study observed that poly(lactic-co-glycolic acid) (PLG or PLGA) scaffolds produced the largest amount of new tissue and vascularization, followed by Matrigel and then fibrin scaffolds[179]. Other studies saw positive tissue ingrowth and vascularization results when using a fibrin-immobilized vascular endothelial growth factor and basic fibroblast growth factor scaffold[180] or a processed bovine cancellous bone-based scaffold[182]. Though prevascularizing constructs within an AV-loop model to then be excised and transplanted to a different location is not associated with high donor site morbidity[176], there have been attempts to fabricate this AV-loop at the desired defect site, which would eliminate any donor morbidity as well as the need for multiple surgeries[183]. In addition to altering the material type used, the incorporation of cells into these scaffold constructs has been investigated. One group found that mesenchymal stem cells would undergo myogenic differentiation over the course of 8 weeks in an axially vascularized AV loop model[184], demonstrating the potential of this technique to be used in regenerative medicine approaches. Over the last two decades, the AV loop approach has shown success both in large animal models[185–191] and, more recently, in the clinic[192]. Together, each of the prevascularization techniques discussed above demonstrates the utility in harnessing the FBR to overcome the hurdle of biomaterial vascularization and fabricate more functional tissue engineering constructs[160].

Harnessing the FBR for in situ tissue engineering

While much of the early work in domesticating the FBR was focused on creating functional structures, more recent work has pivoted to focus on biomolecular utility. As our knowledge around the complex interplay between cells and materials continues to grow, studies have transitioned away from simply trying to minimize fibrotic capsule formation and towards the creation of a seamless tissue-biomaterial interface that might favor integration of the biomaterial with surrounding tissue[193]. Following this thought process, many groups have used the FBR to aid in tissue formation within a scaffold construct for in situ tissue engineering. Much of the in situ tissue engineering field is framed in a very engineering-focused manner (i.e., identifying a defect that needs to be addressed and engineering the best possible material or solution to fill this void). Although precise engineering of material properties is critical, the host response to these implants is also a key component of their success. The FBR to these implanted scaffold constructs enables scaffold remodeling and tissue formation within and around the materials[14]. There are many other variables at play aside from the FBR, and assessing the exact contributions of the FBR is difficult. While many of the papers discussed within this subsection are not explicitly studing the FBR, any implanted material will experience some form of FBR which likely contributes to the outcome. Exemplifying this, studies have shown that the recruitment of host monocytes, which are directly involved in the FBR, plays a pivotal role in the inflammation-mediated remodeling of scaffolds seeded with bone marrow mononuclear cells (BMCs) into a successful tissue engineering graft[194,195]. While we will continue to focus on cell-free scaffolds herein, it is important to note that many studies have used scaffolds seeded with stem cells for in situ tissue engineering purposes. Interestingly, one of the large benefits of integrated stem cells is that they provide immunomodulatory cues for FBR modulation[194–196]. Studies investigating scaffolds seeded with stem cells for in situ tissue engineering applications have shown promise and moved into first-in-human studies in recent years (NCT04467671, a clinical trial evaluating the use of a BMC-seeded tissue-engineered vascular graft)[197–201].

Hernia repair

Despite hernia repair surgery being one of the most commonly performed surgical procedures worldwide[202], rates of intraoperative and postoperative complications remain high[203]. Hernia repair surgeries almost always feature the inclusion of a surgical mesh, most commonly polypropylene, over the weakened muscle with the intention of reinforcing the area. However, these classical meshes do not encourage the regrowth of functional tissue and frequently cause post-surgical adhesions to the surrounding area[203,204]. To remedy these drawbacks, groups have attempted to leverage tissue engineering strategies and the FBR to move towards a more pro-regenerative response, as demonstrated by increased tissue regeneration. One attempt to

improve this mesh resulted in the development of a polypropylene-based 3D multilamellar mesh, ProFlor, that undergoes a more pro-regenerative response to yield higher levels of tissue regeneration than the classical flat hernia meshes. This regenerative difference is thought to be at least partially attributed to the complex "flower" geometry of ProFlor that allows for the mesh to mimic the biomechanics and cyclic loading of the groin area and might encourage improved tissue ingrowth. Interestingly, cyclic loading of macrophage-loaded scaffolds has previously been shown to polarize macrophages towards a more M2-like state[205], which, while not studied in the ProFlor mesh yet, could be a contributing factor in the success of these scaffolds. Additionally, FBGCs were observed within these meshes at a 1-month timepoint[206], indicating that the FBR may have had a role in the outcomes observed. This technology has even been shown efficacious in initial clinical trials (NCT04718298), seemingly decreasing complications and postoperative pain and discomfort[203,207]. Pelvic organ prolapse, a type of hernia, is also a major healthcare issue that negatively affects over 11% of women, with the usage of synthetic hernia meshes resulting in high rates of complications for patients. To meet this need, Hympanova et al. developed electrospun polycaprolactone (PCL) mesh scaffolds modified with ureidopyrimidinone-motifs[208]. This mesh has shown initial promise in a small animal model of surgical reinforcement of a primary musculofascial repair, demonstrating a similar level of compliance to native tissues after being implanted for 42 days. It was observed that there was a higher number of FBGCs around these electrospun meshes as compared to polypropylene implants and a much higher number of M1 macrophages at the site of the polypropylene implants, potentially indicating that these electrospun meshes modulated the FBR. The incorporation of stem cells into scaffolds for similar applications has also been investigated, with studies hoping to explore potential modulation of the FBR caused by the incorporation of these cells. Interestingly, multiple studies found the incorporation of these stem cells to have no significant effect on the early stages of the host response to these cell-containing constructs[209,210].

Musculoskeletal tissue engineering

The repair of skeletal tissues has been a promising area of biological tissue repair for decades and has a plethora of exciting applications[211]. Within this space, one such area of promise is tendon repair via in situ tissue engineering. Li et al. developed a method for tissue repair specifically intended to stimulate the host's remodeling abilities (Fig. 7). They first engineered a PCL-based scaffold with aligned microchannels and implanted this scaffold subcutaneously in rats to allow cells to infiltrate the scaffold. They subsequently explanted the scaffold, removed the PCL template, and decellularized the scaffold material, leaving behind an autologous ECM scaffold with highly aligned microchannels. This ECM-based scaffold was then surgically placed in a rat Achilles tendon defect, and promoted promising regeneration of a neo-tendon[212]. Another area of interest within the skeletal tissue field is bone tissue engineering. Briefly, one group developed an electrospun nanofibrous PCL scaffold functionalized with hydroxyapatite particles for use in in situ bone engineering. They placed this scaffold construct in a calvarial bone defect in a mouse model and saw recruitment of host cells from the bone marrow to the site of the scaffold, resulting in enhanced bone tissue regeneration at the site of the defect[213]. While this study did not explicitly study the role of the FBR on this outcome, it is likely that the inflammatory nature of the FBR that these implanted foreign materials experienced had some impact on the recruitment of cells to the site of this scaffold. Another method used to try to modulate the FBR is via the inclusion of cells in implanted materials. One group found that the inclusion of bone marrow mesenchymal stem cells in scaffold constructs resulted in increased M2-like macrophage polarization[214], likely indicating that the inclusion of these cells played a role in modulating the FBR.

Other advancements in the in situ tissue engineering field

In addition to advancements in the tissue engineering field intended for a specific application, there is work developing scaffolds with instructive niches for more oriented tissue regeneration in situ, which might have applications across many different areas of tissue engineering and regenerative medicine. Similar to the approach developed by Li et al. discussed above, another group engineered ECM-based scaffolds that contain parallel microchannels which are implanted subcutaneously, and then explanted for template removal and decellularization. This decellularized autologous scaffold construct can then be used to guide structured tissue regeneration when placed at the defect site, which they demonstrated in the applications of nerve, artery, and muscle regeneration[215]. For further reading, see reviews discussing in situ tissue engineering in depth[14,216–218].

Harnessing the FBR as a cell attractant mechanism

Previous sections have demonstrated the utility of harnessing the FBR to bring cells to a specific site of interest, primarily for use in tissue engineering applications, many of which have served a structural role. Conversely, this idea of utilizing implanted materials as a method to attract cells to a predefined location has more recently been harnessed to provide cellular and molecular insight for better studying or ameliorating disease burden[100,219,220]. Building upon these concepts, this section will focus on approaches that use the FBR to recruit cells to a localized site to better study or treat disease (Table 1).

Disease diagnosis and pathophysiology

The idea that the FBR changes with disease state has been harnessed for monitoring disease development and progression, including in autoimmunity. For example, porous PCL-based scaffolds were implanted subcutaneously to act as an immunological niche in the experimental autoimmune encephalomyelitis (EAE) mouse model of multiple sclerosis (MS). The FBR recruited immune and stromal cells into the highly porous implant, allowing for the minimally invasive biopsy and analysis of these scaffolds to glean information about the state of the immune system. Implanted scaffolds were used to diagnose disease at presymptomatic time points and showed promise in allowing for the rapid assessment of treatment efficacy[221]. Our group has investigated using the FBR to assess molecular mechanisms of disease. Harnessing the FBR as a source of inflamed tissue in disease models enabled single cell RNA sequencing (scRNAseq) studies to monitor dynamics of cell phenotypes and cell–cell communication in disease without the need for biopsy of vital tissue. Insights from this approach were used to develop a novel nanoparticle-based therapeutic for MS that simultaneously delivered antigen and targeted dysregulated chemokine signaling[222]. Similar work has also been done in the context of diabetes, wherein subcutaneously implanted scaffolds were used as an immunological niche in a mouse model of type 1 diabetes (T1D). Biopsy of these scaffolds and analysis of the cells captured within them were able to successfully delineate healthy mice from diseased mice, providing a potential platform for better diagnosis and further study of T1D[223]. Also in the context of diabetes, Thelin et al. harnessed the FBR to recruit antigen-presenting cells to an implanted scaffold adsorbed with antigen, allowing the scaffold to enrich T cells reactive to the loaded antigen. This system was applied to a diabetes model, wherein it was shown that antigen-loaded scaffolds successfully enriched autoreactive T cells in vivo, allowing for the subsequent harvesting and study of these rare, disease-relevant T cells[224]. Finally, a similar biomaterial niche has been used for the study of organ rejection. This subcutaneously implanted biomaterial scaffold allowed for the minimally invasive study of the body's immune state longitudinally and was able to reliably predict acute rejection of organ allografts in mice[225]. The wide array of use cases discussed here demonstrates the utility of FBR-induced cell recruitment to implanted biomaterial scaffolds for applications in the study and diagnosis of diseases, particularly those of immune dysfunction.

The notion of using scaffolds as a cell attractant mechanism has also been applied to the diagnosis and study of cancer through harnessing scaffolds that are able to recruit both immune and tumor cells post-implantation. This field of research has largely focused on two related avenues of analyzing either captured tumor cells[226] or immune cells[227]. In 2015, Azarin et al. subcutaneously implanted PLG-based microporous

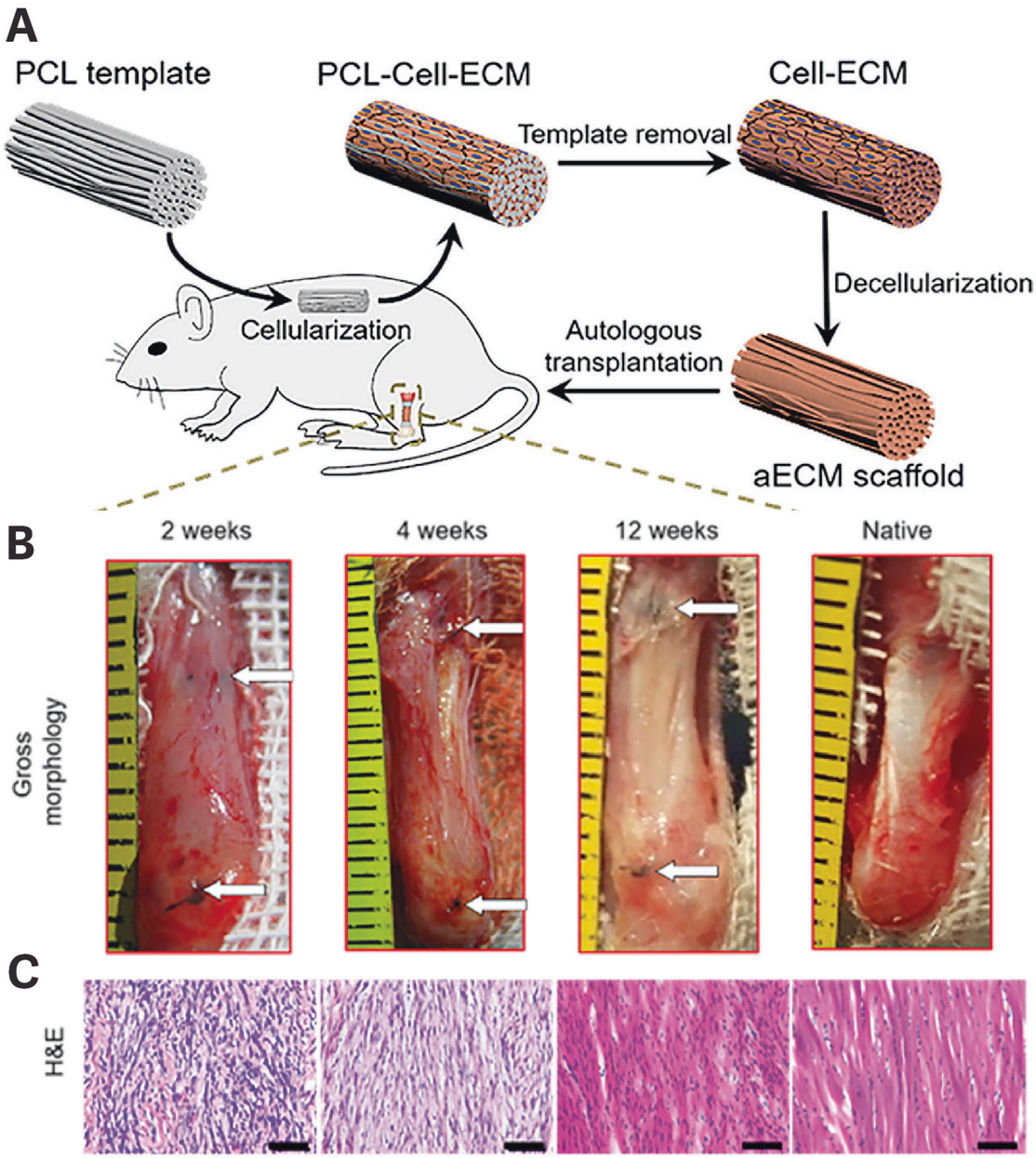

Fig. 7 | The engineering of decellularized autologous extracellular matrix (aECM) scaffolds. A highly aligned PCL template was implanted subcutaneously and allowed to be infiltrated with cells and remodeled in vivo prior to explantation. The PCL template was then removed, and the remaining material was decellularized to leave behind an aECM scaffold with highly aligned microchannels. This aECM scaffold was then used as an autologous scaffold transplantation into a rat Achilles tendon defect, yielding promising tissue remodeling and regeneration in vivo (**A**). The gross morphology (**B**) and H&E staining of sections of the aECM (**C**) are shown at 2 weeks, 4 weeks, and 12 weeks post-implantation, with native tendon as a reference. This figure has been republished with permission[212].

scaffolds in a mouse model of breast cancer to recruit metastatic cancer cells. The authors hypothesized that due to the FBR, the scaffolds would become infiltrated with immune cells, which could condition the site to enable invasion of metastatic cells. Thus, they referred to the implants as metastatic niches. Implanted scaffolds captured high levels of metastatic cells in vivo, allowing for the early detection and further study of metastatic cancer[228]. This work has continued to be improved and expanded since then, improving the stability of the scaffolds by fabricating them out of PCL[229], coating the scaffolds in ECM proteins to increase tumor cell accumulation[230], and further studying the tumor cells recruited to the metastatic niches and how these implanted scaffolds affect the fate and activities of tumor cells[226,231]. More recently, these metastatic niches have been used to provide insights into disease progression and therapeutic outcomes[232,233], identify specific cell populations that are indicative of systemic immune changes driven by different cancer types[234,235], and even probe mechanisms of resistance to the clinically used immune checkpoint blockade therapies[236]. These studies have yielded vital insights into cancer diagnosis, progression, and treatment, as well as continuing to develop an exciting framework that might continue to be applied to other disease models (Fig. 8).

Biomaterial implants also provide a platform for testing different parameters that may influence tumor cells at the scaffold site, including the ECM they encounter upon arrival. One of the important parameters determined to influence the biology of the pre-metastatic niches are focal alterations in the ECM. To synthetically control the expression of ECM at distal sites, polymer implants, like those that were discussed to capture disease-relevant immune cells, were coated with fibronectin and collagen IV proteins prior to implantation[230]. Additionally, diseased organs were screened for

Table 1 | Studies that have leveraged the inflammatory nature of the FBR to recruit immune cells, as well as, in certain cases, cancerous cells, to a predetermined scaffold site for the study or treatment of disease.

Harnessing the FBR as a cell attractant mechanism			
Material	**Disease model**	**Primary purpose**	**Citation number**
Alginate-based azide-conjugated hydrogel as a refillable prodrug depot	Triple negative breast cancer	Treatment of post-resection cancer recurrence	263
Antigen-loaded PLG scaffolds	Hindleg ischemia	Treatment of the ischemic area	244
Decellularized porcine lung, chitosan/gelatin, and poly-L-lactic acid scaffolds	Breast cancer	Developing a 3D in vitro tumor model	235
Degradable porous hyaluronic acid (HA)-based scaffolds loaded with therapeutic cues	4T1 breast cancer	Treatment of disease	262
Mesoporous silica rod (MSR)-based scaffolds loaded with vaccine	Lymphoma	Increase vaccine efficacy	246
Microporous collagen scaffold conjugated with the autoantigen proteolipid protein (PLP)	Experimental autoimmune encephalomyelitis (EAE)	Prevention of disease	245
PCL, chitosan, and montmorillonite clay-based porous drug-eluting scaffold	Breast cancer	Treatment of disease	264
Porous alginate hydrogels loaded with granulocyte-macrophage colony-stimulating factor (GM-CSF)	Healthy mice	Enrichment of dendritic cells in vivo	247
Porous PCL scaffolds	Metastatic breast cancer	Early detection and monitoring of metastasis	224
Porous PCL scaffolds	Metastatic pancreatic cancer	Study of disease	232
Porous PCL scaffolds	Type 1 Diabetes (T1D)	Disease diagnosis	221
Porous PCL scaffolds	EAE	Disease diagnosis and treatment monitoring	219
Porous PCL scaffolds	Metastatic breast cancer	Disease monitoring	230
Porous PCL scaffolds	Triple negative breast cancer	Study of disease and therapeutics	234
Porous PCL scaffolds	Metastatic breast cancer	Early detection and reduction of metastasis	227
Porous PCL scaffolds	Acute cellular allograft rejection	Early prediction of transplant rejection	223
Porous PCL scaffolds	Metastatic breast cancer	Study of disease	233
Porous PCL scaffolds loaded with ECM	Metastatic breast cancer	Study of disease	228
Porous PCL scaffolds and antigen-loaded nanoparticles	EAE	Study and treatment of disease	220
Porous PLG scaffolds	Metastatic breast cancer	Study and treatment of disease	229
Porous PLG scaffolds	Metastatic breast cancer	Early detection of metastasis	226
Porous PLG scaffolds loaded with GM-CSF, danger signals, and cancer antigens	Melanoma	Treatment of disease	249
Porous PLG scaffolds with melanoma tumor lysates and GM-CSF and/or PEI-CpG-rich oligonucleotides (PEI-CpG-ODN)	Melanoma	Treatment of disease	248
Porous PLG scaffolds loaded with antigen	T1D	Study of disease	222
Supported lipid bilayers (SLBs) formed on MSR-based scaffolds	Lymphoma	Treatment of disease	261
Type I collagen-coated inverted colloidal crystal hydrogel scaffolds	Metastatic prostate cancer	Study of disease	237
Urinary bladder matrix scaffold	Melanoma, colon carcinoma, and breast cancer	Treatment of disease	236
Vaccine-loaded polymer-nanoparticle (PNP) hydrogels	Healthy mice (model OVA and TLR3 vaccine)	Increase vaccine efficacy	250
Vaccine-loaded PNP hydrogels	Healthy mice (influenza vaccine)	Increase vaccine efficacy	251
Vaccine-loaded PNP hydrogels	Healthy mice (COVID-19 vaccine)	Increase vaccine efficacy	252
Vaccine-loaded PNP hydrogels	Healthy mice (COVID-19 vaccine)	Increase vaccine efficacy	253
Vaccine-loaded PNP hydrogels	Healthy mice (rabies vaccine)	Minimize the number of vaccine doses needed	254

metastasis-associated factors, which informed the development of a myeloperoxidase coating. Each of these coatings increased the trafficking of tumor cells to the implants, demonstrating the importance of ECM proteins for the recruitment of tumor cells to a predetermined site. Interestingly, the addition of these proteins did not alter the immune cell distribution recruited to the scaffold sites. More recent studies from Li et al. expanded these efforts to focus on differences in 2D vs 3D microenvironments[237], finding that 3D in vitro tumor models can better recapitulate the in vivo tumor microenvironment. In relation to the primary tumor, Wolf et al. presented recent work using tailored ECMs to study the growth and gene expression kinetics of primary tumor development[238]. This mix-and-match approach to manipulating the microenvironment and tumor cells demonstrated an ability to alter infiltrating

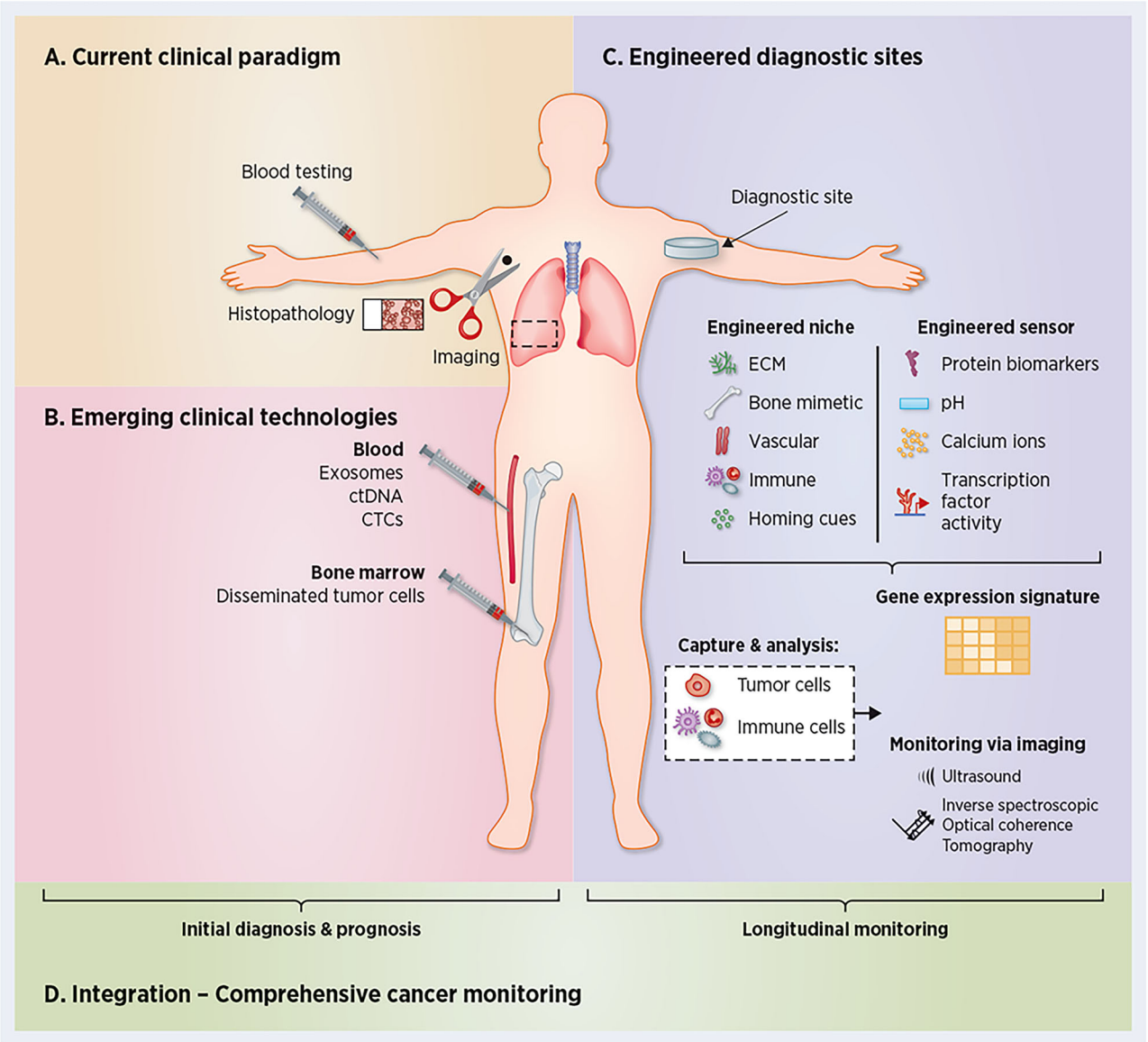

Fig. 8 | In conjunction with the current clinical standards and newly emerging clinical technologies, engineered diagnostic sites should be leveraged as a method to provide unique information over time for the better diagnosis, monitoring, and treatment of cancer. Current clinically used testing methods (**A**) and emerging clinical technologies (**B**) are highlighted as ways to initially diagnose cancer, with engineered scaffold-based diagnostic sites (**C**) as a potential manner of longitudinal monitoring. Integrating these technologies together might allow for more comprehensive cancer diagnosis and monitoring moving forward (**D**). This figure has been republished with permission[233].

immune phenotypes based on insights gleaned from biomaterial-tissue interaction research. Importantly, the results demonstrate that the FBR is progressively altered as a function of disease.

While not explicitly a diagnostic or therapeutic approach, one notable concept that has gained momentum is the use of humanized models for the improvement of therapeutics. A version of these models has recently been used for the modeling of disseminated tumor cells[239]. Scaffolds were pre-seeded with human stromal and immune cells prior to implantation into a mouse model of a tumor xenograft. These scaffolds were found to recruit circulating human tumor cells, providing a platform for the study of post-dissemination phase tumor microenvironments. Additionally, 3D model systems have been developed to better recapitulate tumors in vitro with the goal of personalizing immunotherapies to improve cancer treatment outcomes[240]. Collectively, these examples using humanized and 3D models demonstrate the wide variety of approaches that are being employed to leverage the interactions of implanted materials to improve cancer diagnostics and treatments.

Clinical trials have begun using implanted scaffolds to capture metastatic cells for monitoring disease progression (NCT03085238, completed 2019). While this initial clinical trial did not meet the preset criteria for safety or performance, some of these complications were attributed at least partially to the surgical complexity of this study[241], and therefore might still be a valuable reference moving forward in this field. Additional reviews with information regarding using scaffolds as a premetastatic niche to capture cancer cells or provide a personalized medicine approach to cancer therapeutics can be found elsewhere[242–245].

Disease prevention and treatment

Building upon the work discussed above that has studied diseases and therapeutic approaches, researchers have looked to harness the attributes of the FBR to directly treat diseases. Using a similar technique to the in vivo enrichment of T cells discussed previously[224], Kwee et al. developed an antigen-releasing scaffold that had the capability of locally recruiting and concentrating T_H2 T cells for enhanced vascularization of ischemic tissues,

presenting a novel possibility for the treatment of ischemic diseases[246]. This approach has additionally been applied to the treatment of autoimmune diseases, wherein antigen-specific immune decoys were developed that were intended to mimic tissues that are targeted in autoimmune diseases. Using these decoy scaffolds as a distraction mechanism to selectively intercept autoimmune cells that would otherwise cause damage elsewhere, the subcutaneously implanted scaffolds were seen to result in autoimmune cell sequestration and exhaustion in an EAE mouse model, thus successfully preventing autoimmune disease onset[247].

As mentioned previously, porous polymer-based scaffolds were able to successfully diagnose and further study cancer in mouse models. Interestingly, due to the early recruitment of tumor cells to the site of the subcutaneously implanted scaffolds, these scaffolds significantly reduced disease burden and enhanced survival as compared to the groups that did not receive scaffold implants[228,229]. Additionally, expanding antigen-delivering scaffolds for T cell engagement into cancer treatment[224], it was hypothesized that this technique might lend itself as a potential way to use biomaterials to expand CAR-T cells in situ for the improved treatment of cancer[220]. Together, these studies show promise for the development of new therapies leveraging the FBR to implanted materials for the recruitment, and potential subsequent modulation, of cells at a defined location.

Bulk scaffold-induced FBR to increase vaccine efficacy

As has been highlighted throughout this review, foreign materials elicit a FBR that results in the migration of cells, many of which are immune cells, to the site of the implant. This localized inflammatory environment can be used to modulate immune cells in situ with the goal of increasing vaccine efficacy[101]. The research group of Dr. David Mooney has contributed numerous findings to this area[224,248–251]. In one such study, this group designed mesoporous silica rods that would spontaneously assemble into a bulk material post-injection, acting as a 3D microenvironment for the recruitment of host immune cells. These scaffolds can be loaded with a vaccine, allowing the recruited immune cells to be modulated in vivo at the site of the scaffold before migrating out of the scaffold to further modulate other immune cells, yielding an increase in vaccine efficacy as compared to standard bolus administered vaccines[248]. Similarly, an alginate-based macroporous hydrogel was engineered that slowly released granulocyte-macrophage colony-stimulating factor (GM-CSF) to further increase dendritic cell (DC) recruitment and modulation at the site of the scaffold. While these scaffolds were not yet loaded with a vaccine, they showed high levels of immature DCs recruited to the site of the scaffold, which is a promising platform for future use as a materials-based vaccine delivery platform[249]. In a similar approach, the group developed porous PLG-based scaffolds loaded with various combinations of an inflammatory cytokine, immune danger signal, and tumor lysates to act as tumor-mimicking materials that effectively worked as a cancer vaccine. They found that these scaffolds, when implanted subcutaneously, successfully recruited and activated DCs in situ, generating cytotoxic T cells against cancer cells that were able to mediate tumor regression in a mouse model[250,251]. This technology has moved into stage I clinical trials for the treatment of metastatic melanoma (NCT01753089), indicating promise for antigen-loaded material-based therapies in the future[224].

Dr. Eric Appel's research group has also significantly contributed many findings in this area[252–256], leveraging the development of a local inflammatory niche within a foreign material and extended subunit vaccine release from scaffolds. Briefly, a polymer-based injectable hydrogel material was developed that was able to deliver multiple distinct vaccine components over extended periods. The local inflammatory environment, combined with the sustained delivery of vaccine subunits, resulted in enhanced humoral immunity as compared to standard bolus vaccine immunizations[252]. This system has further proven efficacious in a mouse model testing the influenza vaccine[253]. More recently, this system has been applied to the coronavirus disease (COVID-19) vaccine, showing that this hydrogel-based slow release of a receptor-binding domain subunit vaccine was able to elicit neutralizing antibody responses against SARS-CoV-2, whereas bolus vaccines did not[254]. Interestingly, it was further shown that using this prolonged release hydrogel system only a single immunization was required to achieve broad and durable immunity, as opposed to the multiple rounds of boosting required by the standard COVID-19 vaccine[255]. Together, this work demonstrates that biomaterials-based strategies for prolonged vaccine exposure might minimize the need for repeated vaccine doses and complex immunization schedules that are often expensive and challenging to maintain in under-resourced environments[256].

Almost all clinically used anti-cancer therapeutics have the significant drawbacks of needing to be delivered systemically, and consequently having broad-spectrum toxicity to healthy host cells in addition to the targeted cancer cells[257]. Implantable immunotherapies have been designed with this limitation in mind, wherein these therapies are intended to localize immunogenic cues to the specific site of the cancer cells[258]. One of the most prevalent uses of biomaterial implants in the cancer therapy space has been the controlled release of therapeutics[259], and more recently, the localization of antigens and adjuvants to induce a specific immunogenic response against tumors[220,260,261]. These immunotherapies have recently entered early-stage clinical trials (NCT04062721—assessing local immunomodulation via a thermoreversible hydrogel)[258,262]. Recent designs for the development of implantable cancer vaccines have relied on the attraction of innate immune cells and delivered a milieu of costimulatory and informational cues[263]. In addition to the concept of implanting a scaffold with cues for a vaccine, another common theme has been the incorporation of therapeutics in implanted scaffolds that can be inserted into the surgical site following resection of a primary tumor[264,265]. Within the space of bone metastases, researchers have developed biomaterials that leverage the material–tissue interaction to rebuild lost bone while also releasing anti-cancer compounds to prevent tumor recurrence[266].

Of note, there has also been work focusing on the impact of a localized FBR on distal aspects of cancer. One interesting report demonstrated that the implantation of a polymer scaffold, free from any additional adjuvants, altered the phenotype of macrophages in the primary tumor[231]. This illustrates that while the FBR is generally thought of as a localized response to introduced foreign bodies, it might be able to disrupt the kinetics of systemic immunological diseases like cancer metastasis[231] or otherwise be modulated in response to disease or infection[28,29].

Additional details regarding leveraging biomaterials as local niches for the modulation of immune cells in situ can be found elsewhere[101,267].

Conclusion and outlook

The FBR is a complex phenomenon that occurs when a foreign material is introduced to the body, yielding an immune response that attempts to dispose of or encapsulate the implanted material. Historically, the FBR has been described as a negative outcome to the implantation of foreign materials and thus a reaction that needed to be minimized as much as possible to prevent the failure of implanted medical devices. Due to this, a plethora of different methods for mitigating the FBR have been developed throughout the years and continue to be studied today. Yet, the paradigm of the FBR as a negative reaction has begun to be challenged as many different technologies have emerged that harness the FBR as a useful tool.

The FBR has been consistently viewed as a deleterious response to implanted materials, but in this review, we propose a rebrand. The FBR goes well beyond the dogma of a static inflammatory response that simply walls off a material. It is a dynamic process involving varied cells, signaling molecules, and ECM deposition that can be harnessed for myriad applications. We propose that the FBR instead be thought of as a response that can be tuned and leveraged, if desired. The FBR may at times still be a consequence with no specific intention. However, the FBR could also be utilized with the specific intention of enabling in situ tissue engineering, for example. This will move the field past cause and further towards precision control.

Highlighting studies that examine positive aspects of the FBR, this review discusses work across in vivo tissue engineering, in situ tissue engineering, and disease-ameliorating implants. The FBR has the potential to

help provide solutions to many of medicine's largest limitations, such as providing an autologous and tunable tissue source, prevascularizing tissue engineering constructs, and providing a minimally invasive way to collect diagnostic information about the current state of the immune system. Studies are just recently starting to unveil the interconnected relationship between disease state, the FBR, and the types of materials being implanted. The FBR remains an extremely powerful response to introduced foreign bodies that will continue to be modified and leveraged as an invaluable tool as the intricacies of this response continue to be unveiled.

Data availability

No datasets were generated or analyzed during the current study.

Received: 27 February 2025; Accepted: 9 November 2025;
Published online: 16 January 2026

References

1. Anderson, J. M., Rodriguez, A. & Chang, D. T. Foreign body reaction to biomaterials. *Semin. Immunol.* **20**, 86–100 (2008).
2. Chandorkar, Y., K, R. & Basu, B. The foreign body response demystified. *ACS Biomater. Sci. Eng.* **5**, 19–44 (2019).
3. Luttikhuizen, D. T., Harmsen, M. C. & Luyn, M. J. A. V. Cellular and molecular dynamics in the foreign body reaction. *Tissue Eng*. **12**, 1955–1970 (2006).
4. Veiseh, O. & Vegas, A. J. Domesticating the foreign body response: Recent advances and applications. *Adv. Drug Deliv. Rev.* **144**, 148–161 (2019).
5. Carnicer-Lombarte, A., Chen, S.-T., Malliaras, G. G. & Barone, D. G. Foreign body reaction to implanted biomaterials and its impact in nerve neuroprosthetics. *Front. Bioeng. Biotechnol*. **9**, 6622524 (2021).
6. Morais, J. M., Papadimitrakopoulos, F. & Burgess, D. J. Biomaterials/tissue interactions: possible solutions to overcome foreign body response. *AAPS J* **12**, 188–196 (2010).
7. Major, M. R., Wong, V. W., Nelson, E. R., Longaker, M. T. & Gurtner, G. C. The foreign body response: at the interface of surgery and bioengineering. *Plast. Reconstr. Surg.* **135**, 1489 (2015).
8. Ward, W. K. A review of the foreign-body response to subcutaneously-implanted devices: the role of macrophages and cytokines in biofouling and fibrosis. *J. Diabetes Sci. Technol*. **2**, 768–777 (2008).
9. Franz, S., Rammelt, S., Scharnweber, D. & Simon, J. C. Immune responses to implants—a review of the implications for the design of immunomodulatory biomaterials. *Biomaterials* **32**, 6692–6709 (2011).
10. Hu, W.-J., Eaton, J., Ugarova, T. & Tang, L. Molecular basis of biomaterial-mediated foreign body reactions. *Blood* **98**, 1231–1238 (2001).
11. Wilson, C. J., Clegg, R. E., Leavesley, D. I. & Pearcy, M. J. Mediation of biomaterial–cell interactions by adsorbed proteins: a review. *Tissue Eng.* **11**, 1–18 (2005).
12. Xu, L.-C. & Siedlecki, C. A. Effects of surface wettability and contact time on protein adhesion to biomaterial surfaces. *Biomaterials* **28**, 3273–3283 (2007).
13. Macias, S. L. & Keselowsky, B. G. Perspectives on immunometabolism at the biomaterials interface. *Mol. Aspects Med.* **83**, 100992 (2022).
14. Smits, A. I. P. M. & Bouten, C. V. C. Tissue engineering meets immunoengineering: prospective on personalized in situ tissue engineering strategies. *Curr. Opin. Biomed. Eng.* **6**, 17–26 (2018).
15. Murray, P. J. Macrophage polarization. *Annu. Rev. Physiol.* **79**, 541–566 (2017).
16. Mosser, D. M. & Edwards, J. P. Exploring the full spectrum of macrophage activation. *Nat. Rev. Immunol.* **8**, 958–969 (2008).
17. Mantovani, A. et al. The chemokine system in diverse forms of macrophage activation and polarization. *Trends Immunol.* **25**, 677–686 (2004).
18. Lawrence, T. & Natoli, G. Transcriptional regulation of macrophage polarization: enabling diversity with identity. *Nat. Rev. Immunol.* **11**, 750–761 (2011).
19. Sridharan, R., Cameron, A. R., Kelly, D. J., Kearney, C. J. & O'Brien, F. J. Biomaterial based modulation of macrophage polarization: a review and suggested design principles. *Mater. Today* **18**, 313–325 (2015).
20. Hinz, B. et al. The myofibroblast: one function, multiple origins. *Am. J. Pathol.* **170**, 1807–1816 (2007).
21. Cai, F., Jiang, B. & He, F. Formation and biological activities of foreign body giant cells in response to biomaterials. *Acta Biomater.* **188**, 1–26 (2024).
22. Zhao, Q. et al. Foreign-body giant cells and polyurethane biostability: In vivo correlation of cell adhesion and surface cracking. *J. Biomed. Mater. Res.* **25**, 177–183 (1991).
23. Liang, N. E. et al. Understanding the foreign body response via single-cell meta-analysis. *Biology* **13**, 540 (2024).
24. Headon, H., Kasem, A. & Mokbel, K. Capsular contracture after breast augmentation: an update for clinical practice. *Arch. Plast. Surg.* **42**, 532–543 (2022).
25. Salatino, J. W., Ludwig, K. A., Kozai, T. D. Y. & Purcell, E. K. Glial responses to implanted electrodes in the brain. *Nat. Biomed. Eng.* **1**, 862–877 (2017).
26. Spearman, B. S. et al. Tissue-engineered peripheral nerve interfaces. *Adv. Funct. Mater.* **28**, 1701713 (2018).
27. Dondossola, E. et al. Examination of the foreign body response to biomaterials by nonlinear intravital microscopy. *Nat. Biomed. Eng.* **1**, 1–10 (2016).
28. Yang, B. et al. Murine gut microbiota dysbiosis via enteric infection modulates the foreign body response to a distal biomaterial implant. *Proc. Natl. Acad. Sci* **122**, e2422169122 (2025).
29. Soto, R. J., Merricks, E. P., Bellinger, D. A., Nichols, T. C. & Schoenfisch, M. H. Influence of diabetes on the foreign body response to nitric oxide-releasing implants. *Biomaterials* **157**, 76–85 (2018).
30. Brown, B. N., Haschak, M. J., Lopresti, S. T. & Stahl, E. C. Effects of age-related shifts in cellular function and local microenvironment upon the innate immune response to implants. *Semin. Immunol.* **29**, 24–32 (2017).
31. Hachim, D. et al. Effects of aging upon the host response to implants. *J. Biomed. Mater. Res. A* **105**, 1281–1292 (2017).
32. Boersema, G. S. A. et al. Monocyte subsets in blood correlate with obesity related response of macrophages to biomaterials in vitro. *Biomaterials* **109**, 32–39 (2016).
33. Orellano, L. A. A. et al. Upregulation of foreign body response in obese mice. *Obes. Silver Spring Md* **26**, 531–539 (2018).
34. O'Shea, T. M. et al. Foreign body responses in mouse central nervous system mimic natural wound responses and alter biomaterial functions. *Nat. Commun.* **11**, 6203 (2020).
35. Oakes, R. S., Polei, M. D., Skousen, J. L. & Tresco, P. A. An astrocyte derived extracellular matrix coating reduces astrogliosis surrounding chronically implanted microelectrode arrays in rat cortex. *Biomaterials* **154**, 1–11 (2018).
36. Luttikhuizen, D. T. et al. The correlation between difference in foreign body reaction between implant locations and cytokine and MMP expression. *Biomaterials* **27**, 5763–5770 (2006).
37. Oliva, N. et al. Regulation of dendrimer:dextran material performance by altered tissue microenvironment in inflammation and neoplasia. *Sci. Transl. Med.* **7**, 272ra11 (2015).
38. Capuani, S., Malgir, G., Chua, C. Y. X. & Grattoni, A. Advanced strategies to thwart foreign body response to implantable devices. *Bioeng. Transl. Med.* **7**, e10300 (2022).
39. Zhang, D. et al. Dealing with the foreign-body response to implanted biomaterials: strategies and applications of new materials. *Adv. Funct. Mater.* **31**, 2007226 (2021).

40. Onuki, Y., Bhardwaj, U., Papadimitrakopoulos, F. & Burgess, D. J. A review of the biocompatibility of implantable devices: current challenges to overcome foreign body response. *J. Diabetes Sci. Technol.* **2**, 1003–1015 (2008).
41. Kämmerling, L. et al. Mitigating the foreign body response through 'immune-instructive' biomaterials. *J. Immunol. Regen. Med.* **12**, 100040 (2021).
42. Morris, A. H., Stamer, D. K. & Kyriakides, T. R. The host response to naturally-derived extracellular matrix biomaterials. *Semin. Immunol.* **29**, 72–91 (2017).
43. Dearth, C. L., Keane, T. J., Scott, J. R., Daly, K. A. & Badylak, S. F. A rodent model to evaluate the tissue response to a biological scaffold when adjacent to a synthetic material. *Tissue Eng. Part A* **21**, 2526–2535 (2015).
44. Faulk, D. M. et al. ECM hydrogel coating mitigates the chronic inflammatory response to polypropylene mesh. *Biomaterials* **35**, 8585–8595 (2014).
45. Wolf, M. T. et al. Macrophage polarization in response to ECM coated polypropylene mesh. *Biomaterials* **35**, 6838–6849 (2014).
46. Brodbeck, W. G. et al. In vivo leukocyte cytokine mRNA responses to biomaterials are dependent on surface chemistry. *J. Biomed. Mater. Res. A* **64A**, 320–329 (2003).
47. Lee, J. H., Khang, G., Lee, J. W. & Lee, H. B. Interaction of different types of cells on polymer surfaces with wettability gradient. *J. Colloid Interface Sci.* **205**, 323–330 (1998).
48. Xie, X. et al. Reduction of measurement noise in a continuous glucose monitor by coating the sensor with a zwitterionic polymer. *Nat. Biomed. Eng.* **2**, 894–906 (2018).
49. Zhang, L. et al. Zwitterionic hydrogels implanted in mice resist the foreign-body reaction. *Nat. Biotechnol.* **31**, 553–556 (2013).
50. Chen, W.-H., Liao, T.-Y., Thissen, H. & Tsai, W.-B. One-step aminomalononitrile-based coatings containing zwitterionic copolymers for the reduction of biofouling and the foreign body response. *ACS Biomater. Sci. Eng.* **5**, 6454–6462 (2019).
51. Liu, Q. et al. Zwitterionically modified alginates mitigate cellular overgrowth for cell encapsulation. *Nat. Commun.* **10**, 5262 (2019).
52. Lopez-Silva, T. L. et al. Chemical functionality of multidomain peptide hydrogels governs early host immune response. *Biomaterials* **231**, 119667 (2020).
53. Hou, Y. et al. Therapeutic protein PEPylation: the helix of nonfouling synthetic polypeptides minimizes antidrug antibody generation. *ACS Cent. Sci.* **5**, 229–236 (2019).
54. Zhang, P. et al. Polypeptides with high zwitterion density for safe and effective therapeutics. *Angew. Chem.* **130**, 7869–7873 (2018).
55. Doloff, J. C. et al. The surface topography of silicone breast implants mediates the foreign body response in mice, rabbits and humans. *Nat. Biomed. Eng.* **5**, 1115–1130 (2021).
56. Mesa-Restrepo, A. et al. Osteointegration of Ti bone implants: a study on how surface parameters control the foreign body response. *ACS Biomater. Sci. Eng.* **10**, 4662–4681 (2024).
57. Chen, Y. et al. Decoding the "Fingerprint" of implant materials: insights into the foreign body reaction. *Small* **20**, 2310325 (2024).
58. Kyle, D. J. T., Oikonomou, A., Hill, E. & Bayat, A. Development and functional evaluation of biomimetic silicone surfaces with hierarchical micro/nano-topographical features demonstrates favourable in vitro foreign body response of breast-derived fibroblasts. *Biomaterials* **52**, 88–102 (2015).
59. Matlaga, B. F., Yasenchak, L. P. & Salthouse, T. N. Tissue response to implanted polymers: the significance of sample shape. *J. Biomed. Mater. Res.* **10**, 391–397 (1976).
60. Salthouse, T. N. Some aspects of macrophage behavior at the implant interface. *J. Biomed. Mater. Res.* **18**, 395–401 (1984).
61. Veiseh, O. et al. Size- and shape-dependent foreign body immune response to materials implanted in rodents and non-human primates. *Nat. Mater.* **14**, 643–651 (2015).
62. Ward, W. K., Slobodzian, E. P., Tiekotter, K. L. & Wood, M. D. The effect of microgeometry, implant thickness and polyurethane chemistry on the foreign body response to subcutaneous implants. *Biomaterials* **23**, 4185–4192 (2002).
63. Schoberleitner, I. et al. Is it all about surface topography? An intra-individual clinical outcome analysis of two different implant surfaces in breast reconstruction. *J. Clin. Med.* **12**, 1315 (2023).
64. Papenburg, B. J. et al. One-step fabrication of porous micropatterned scaffolds to control cell behavior. *Biomaterials* **28**, 1998–2009 (2007).
65. Madden, L. R. et al. Proangiogenic scaffolds as functional templates for cardiac tissue engineering. *Proc. Natl. Acad. Sci. USA* **107**, 15211–15216 (2010).
66. Sussman, E. M., Halpin, M., Muster, J., Moon, R. & Ratner, B. D. Porous implants modulate healing and induce shifts in local macrophage polarization in the foreign body reaction. *Ann. Biomed. Eng.* **42**, 1508–1516 (2014).
67. Ratner, B. D. The biocompatibility manifesto: biocompatibility for the twenty-first century. *J Cardiovasc. Transl. Res.* **4**, 523–527 (2011).
68. Gancedo, M., Ruiz-Corro, L., Salazar-Montes, A., Rincón, A. R. & Armendáriz-Borunda, J. Pirfenidone prevents capsular contracture after mammary implantation. *Aesthetic Plast. Surg.* **32**, 32–40 (2008).
69. Wu, P. & Grainger, D. W. Drug/device combinations for local drug therapies and infection prophylaxis. *Biomaterials* **27**, 2450–2467 (2006).
70. Morris, A. H., Mahal, R. S., Udell, J., Wu, M. & Kyriakides, T. R. Multicompartment drug release system for dynamic modulation of tissue responses. *Adv. Healthc. Mater.* **6**, 1700370 (2017).
71. Patil, S. D., Papadimitrakopoulos, F. & Burgess, D. J. Dexamethasone-loaded poly(lactic-co-glycolic) acid microspheres/poly(vinyl alcohol) hydrogel composite coatings for inflammation control. *Diabetes Technol. Ther.* **6**, 887–897 (2004).
72. Gu, B., Papadimitrakopoulos, F. & Burgess, D. J. PLGA microsphere/PVA hydrogel coatings suppress the foreign body reaction for 6 months. *J. Controlled Release* **289**, 35–43 (2018).
73. Rahman, M. T. et al. Dexamethasone-eluting cochlear implants reduce inflammation and foreign body response in human and murine cochleae. *Sci. Rep.* **15**, 30615 (2025).
74. Patil, S. D., Papadmitrakopoulos, F. & Burgess, D. J. Concurrent delivery of dexamethasone and VEGF for localized inflammation control and angiogenesis. *J. Controlled Release* **117**, 68–79 (2007).
75. Brandt, C. J., Kammer, D., Fiebeler, A. & Klinge, U. Beneficial effects of hydrocortisone or spironolactone coating on foreign body response to mesh biomaterial in a mouse model. *J. Biomed. Mater. Res. A* **99A**, 335–343 (2011).
76. Bhardwaj, U., Sura, R., Papadimitrakopoulos, F. & Burgess, D. J. PLGA/PVA hydrogel composites for long-term inflammation control following s.c. implantation. *Int. J. Pharm.* **384**, 78–86 (2010).
77. van Putten, S. M., Wübben, M., Hennink, W. E., van Luyn, M. J. A. & Harmsen, M. C. The downmodulation of the foreign body reaction by cytomegalovirus encoded interleukin-10. *Biomaterials* **30**, 730–735 (2009).
78. Qian, Y. et al. Surface modification of nanofibrous matrices via layer-by-layer functionalized silk assembly for mitigating the foreign body reaction. *Biomaterials* **164**, 22–37 (2018).
79. Rujitanaroj, P. et al. Controlling fibrous capsule formation through long-term down-regulation of collagen type I (COL1A1) expression by nanofiber-mediated siRNA gene silencing. *Acta Biomater* **9**, 4513–4524 (2013).
80. Takahashi, H., Wang, Y. & Grainger, D. W. Device-based local delivery of siRNA against mammalian target of rapamycin (mTOR) in a murine subcutaneous implant model to inhibit fibrous encapsulation. *J. Controlled Release* **147**, 400–407 (2010).
81. Farah, S. et al. Long-term implant fibrosis prevention in rodents and non-human primates using crystallized drug formulations. *Nat. Mater.* **18**, 892–904 (2019).

82. Hachim, D. et al. Distinct macrophage populations and phenotypes associated with IL-4 mediated immunomodulation at the host implant interface. *Biomater. Sci.* **8**, 5751–5762 (2020).
83. Roosa, C. A. et al. Conjugation of IL-33 to microporous annealed particle scaffolds enhances type 2-like immune responses in vitro and in vivo. *Adv. Healthc. Mater.* **13**, 2400249 (2024).
84. Whyte, W. et al. Dynamic actuation enhances transport and extends therapeutic lifespan in an implantable drug delivery platform. *Nat. Commun.* **13**, 4496 (2022).
85. Tang, X., Shen, H., Zhao, S., Li, N. & Liu, J. Flexible brain–computer interfaces. *Nat. Electron.* **6**, 109–118 (2023).
86. Dolan, E. B. et al. An actuatable soft reservoir modulates host foreign body response. *Sci. Robot.* **4**, eaax7043 (2019).
87. Padmanabhan, J. et al. Allometrically scaling tissue forces drive pathological foreign-body responses to implants via Rac2-activated myeloid cells. *Nat. Biomed. Eng.* **7**, 1419–1436 (2023).
88. Bryda, E. C. The mighty mouse: the impact of rodents on advances in biomedical research. *Mo. Med.* **110**, 207–211 (2013).
89. Vegas, A. J. et al. Combinatorial hydrogel library enables identification of materials that mitigate the foreign body response in primates. *Nat. Biotechnol.* **34**, 345–352 (2016).
90. Doloff, J. C. et al. Colony stimulating factor-1 receptor is a central component of the foreign body response to biomaterial implants in rodents and non-human primates. *Nat. Mater.* **16**, 671–680 (2017).
91. King, A., Sandler, S. & Andersson, A. The effect of host factors and capsule composition on the cellular overgrowth on implanted alginate capsules. *J. Biomed. Mater. Res.* **57**, 374–383 (2001).
92. Doloff, J. C. et al. Identification of a humanized mouse model for functional testing of immune-mediated biomaterial foreign body response. *Sci. Adv.* **9**, eade9488 (2023).
93. Wu, J. et al. Adhesive anti-fibrotic interfaces on diverse organs. *Nature* **630**, 360–367 (2024).
94. Walsh, N. C. et al. Humanized mouse models of clinical disease. *Annu. Rev. Pathol. Mech. Dis.* **12**, 187–215 (2017).
95. Chuprin, J. et al. Humanized mouse models for immuno-oncology research. *Nat. Rev. Clin. Oncol.* **20**, 192–206 (2023).
96. Morris, A. H., Hughes, K. R. & Shea, L. D. 3-Nanotechnology and biomaterials for immune modulation and monitoring. in *Immunomodulatory Biomaterials* (eds Badylak, S. F. & Elisseeff, J. H.) 41–65 (Woodhead Publishing, 2021); https://doi.org/10.1016/B978-0-12-821440-4.00001-3.
97. Whitaker, R., Hernaez-Estrada, B., Hernandez, R. M., Santos-Vizcaino, E. & Spiller, K. L. Immunomodulatory biomaterials for tissue repair. *Chem. Rev.* **121**, 11305–11335 (2021).
98. ten Brink, T., Damanik, F., Rotmans, J. I. & Moroni, L. Unraveling and harnessing the immune response at the cell–biomaterial interface for tissue engineering purposes. *Adv. Healthc. Mater.* **13**, 2301939 (2024).
99. Sparks, C. H. Autogenous grafts made to order. *Ann. Thorac. Surg.* **8**, 104–113 (1969).
100. Ali, O. A. & Mooney, D. J. Immunologically active biomaterials for cancer therapy. in *Cancer Immunology and Immunotherapy* (ed. Dranoff, G.) 279–297 (Springer, Berlin, 2011); https://doi.org/10.1007/82_2010_69.
101. Roth, G. A. et al. Designing spatial and temporal control of vaccine responses. *Nat. Rev. Mater.* **7**, 174–195 (2022).
102. Wood, K. J. & Goto, R. Mechanisms of rejection: current perspectives. *Transplantation* **93**, 1–10 (2012).
103. Salthouse, D., Novakovic, K., Hilkens, C. M. U. & Ferreira, A. M. Interplay between biomaterials and the immune system: Challenges and opportunities in regenerative medicine. *Acta Biomater* **155**, 1–18 (2023).
104. Eiken, O. Autogenous connective tissue tubes for replacement of small artery defects. A preliminary report of an experimental study in dogs. *Acta Chir. Scand.* **120**, 47–50 (1960).
105. Sparks, C. H. Die-grown reinforced arterial grafts: observations on long-term animal grafts and clinical experience. *Ann. Surg.* **172**, 787–794 (1970).
106. Sparks, C. H. Silicone mandril method for growing reinforced autogenous femoro-popliteal artery grafts in situ. *Ann. Surg.* **177**, 293–300 (1973).
107. Hallin, R. W. Complications with the mandril-grown (Sparks) dacron arterial graft. *Am. Surg.* **41**, 550–554 (1975).
108. Hallin, R. W. & Sweetman, W. R. The Sparks' mandril graft: a seven year follow-up of mandril grafts placed by Charles H. Sparks and his associates. *Am. J. Surg.* **132**, 221–223 (1976).
109. Roberts, P. N. & Hopkinson, B. R. The Sparks mandril in femoropopliteal bypass. *Br. Med. J.* **2**, 1190–1191 (1977).
110. Guidoin, R. et al. The Sparks-Mandril arterial prosthesis. An ingenious concept, a total failure. What can we learn from it? *J. Mal. Vasc.* **9**, 277–283 (1984).
111. Campbell, J. H., Efendy, J. L. & Campbell, G. R. Novel vascular graft grown within recipient's own peritoneal cavity. *Circ. Res*. https://doi.org/10.1161/01.RES.85.12.1173 (1999).
112. Chue, W.-L. et al. Dog peritoneal and pleural cavities as bioreactors to grow autologous vascular grafts. *J. Vasc. Surg.* **39**, 859–867 (2004).
113. Rothuizen, T. C. et al. Tailoring the foreign body response for in situ vascular tissue engineering. *Tissue Eng. Part C Methods* **21**, 436–446 (2015).
114. Rothuizen, T. C. et al. Development and evaluation of in vivo tissue engineered blood vessels in a porcine model. *Biomaterials* **75**, 82–90 (2016).
115. Bezhaeva, T. et al. Contribution of bone marrow-derived cells to in situ engineered tissue capsules in a rat model of chronic kidney disease. *Biomaterials* **194**, 47–56 (2019).
116. Geelhoed, W. J. et al. A novel method for engineering autologous non-thrombogenic in situ tissue-engineered blood vessels for arteriovenous grafting. *Biomaterials* **229**, 119577 (2020).
117. Zhi, D. et al. Mechanically reinforced biotubes for arterial replacement and arteriovenous grafting inspired by architectural engineering. *Sci. Adv*. https://doi.org/10.1126/sciadv.abl3888 (2022).
118. Su, Z., Xing, Y., Wang, F., Xu, Z. & Gu, Y. Biological small-calibre tissue engineered blood vessels developed by electrospinning and in-body tissue architecture. *J. Mater. Sci. Mater. Med.* **33**, 67 (2022).
119. Yan, H. et al. Functionalization of in vivo tissue-engineered living biotubes enhance patency and endothelization without the requirement of systemic anticoagulant administration. *Bioact. Mater.* **26**, 292–305 (2023).
120. Nakayama, Y., Ishibashi-Ueda, H. & Takamizawa, K. In vivo tissue-engineered small-caliber arterial graft prosthesis consisting of autologous tissue (biotube). *Cell Transplant* **13**, 439–450 (2004).
121. Watanabe, T., Kanda, K., Ishibashi-Ueda, H., Yaku, H. & Nakayama, Y. Autologous small-caliber "Biotube" vascular grafts with argatroban loading: a histomorphological examination after implantation to rabbits. *J. Biomed. Mater. Res. B Appl. Biomater.* **92B**, 236–242 (2010).
122. Yamanami, M. et al. Implantation study of small-caliber "biotube" vascular grafts in a rat model. *J. Artif. Organs* **16**, 59–65 (2013).
123. Furukoshi, M., Moriwaki, T. & Nakayama, Y. Development of an in vivo tissue-engineered vascular graft with designed wall thickness (biotube type C) based on a novel caged mold. *J. Artif. Organs* **19**, 54–61 (2016).
124. Kato, N. et al. First successful clinical application of the in vivo tissue-engineered autologous vascular graft. *Ann. Thorac. Surg.* **102**, 1387–1390 (2016).
125. Nakayama, Y. et al. Pre-implantation evaluation of a small-diameter, long vascular graft (Biotube®) for below-knee bypass surgery in goats. *J. Biomed. Mater. Res. B Appl. Biomater.* **110**, 2387–2398 (2022).

126. Nakayama, Y. et al. iBTA-induced biotube® blood vessels: 2020 update. *Kidney Dial* **1**, 3–13 (2021).
127. Nakayama, Y., Furukoshi, M., Terazawa, T. & Iwai, R. Development of long in vivo tissue-engineered "Biotube" vascular grafts. *Biomaterials* **185**, 232–239 (2018).
128. Higashita, R., Miyazaki, M., Oi, M. & Ishikawa, N. First-in-human results of an in-body tissue architecture-induced tissue-engineered vascular graft "Biotube" for application in distal bypass for chronic limb-threatening ischemia. *J. Vasc. Surg. Cases Innov. Tech.* **8**, 488–493 (2022).
129. Shuto, T. et al. Safety and efficacy of an iBTA-induced autologous Biotube® vascular graft and its preparation device BTM1 in below-the-knee bypass surgery for chronic limb threatening ischemia: a protocol for an open-label, single-arm, multicenter clinical trial. *PLOS ONE* 20(11) (2025).
130. Ratner, B. Vascular grafts: technology success/technology failure. *BME Front* **4**, 0003 (2023).
131. Fang, S., Ellman, D. G. & Andersen, D. C. Review: tissue engineering of small-diameter vascular grafts and their in vivo evaluation in large animals and humans. *Cells* **10**, 713 (2021).
132. Durán-Rey, D., Crisóstomo, V., Sánchez-Margallo, J. A. & Sánchez-Margallo, F. M. Systematic review of tissue-engineered vascular grafts. *Front. Bioeng. Biotechnol*. **9**, 771400 (2021).
133. Geelhoed, W. J., Moroni, L. & Rotmans, J. I. Utilizing the foreign body response to grow tissue engineered blood vessels in vivo. *J Cardiovasc. Transl. Res.* **10**, 167–179 (2017).
134. Wang, X. et al. Nonlinear elasticity of blood vessels and vascular grafts. *ACS Biomater*. *Sci*. *Eng*. https://doi.org/10.1021/acsbiomaterials.4c00326 (2024).
135. Masquelet, A. C. & Begue, T. The concept of induced membrane for reconstruction of long bone defects. *Orthop. Clin.* **41**, 27–37 (2010).
136. Pelissier, P. H., Masquelet, A. C., Bareille, R., Pelissier, S. M. & Amedee, J. Induced membranes secrete growth factors including vascular and osteoinductive factors and could stimulate bone regeneration. *J. Orthop. Res.* **22**, 73–79 (2004).
137. Giannoudis, P. V., Jones, E. & Einhorn, T. A. Fracture healing and bone repair. *Injury* **42**, 549–550 (2011).
138. Mathieu, L. et al. Masquelet technique in military practice: specificities and future directions for combat-related bone defect reconstruction. *Mil. Med. Res.* **9**, 48 (2022).
139. Pelissier, P., Martin, D., Baudet, J., Lepreux, S. & Masquelet, A.-C. Behaviour of cancellous bone graft placed in induced membranes. *Br. J. Plast. Surg.* **55**, 596–598 (2002).
140. Viateau, V. et al. Induction of a barrier membrane to facilitate reconstruction of massive segmental diaphyseal bone defects: an ovine model. *Vet. Surg.* **35**, 445–452 (2006).
141. Masquelet, A. C. Induced membrane technique: pearls and pitfalls. *J. Orthop. Trauma* **31**, S36 (2017).
142. Alford, A. I., Nicolaou, D., Hake, M. & McBride-Gagyi, S. Masquelet's induced membrane technique: review of current concepts and future directions. *J. Orthop. Res.* **39**, 707–718 (2021).
143. Taylor, B. C., French, B. G., Fowler, T. T., Russell, J. & Poka, A. Induced membrane technique for reconstruction to manage bone loss. *JAAOS J. Am. Acad. Orthop. Surg.* **20**, 142 (2012).
144. Masquelet, A. C. The induced membrane technique. *Orthop. Traumatol. Surg. Res.* **106**, 785–787 (2020).
145. Taylor, B. C., Hancock, J., Zitzke, R. & Castaneda, J. Treatment of bone loss with the induced membrane technique: techniques and outcomes. *J. Orthop. Trauma* **29**, 554 (2015).
146. Mauffrey, C., Hake, M. E., Chadayammuri, V. & Masquelet, A.-C. Reconstruction of long bone infections using the induced membrane technique: tips and tricks. *J. Orthop. Trauma* **30**, e188 (2016).
147. Han, W. et al. Induced membrane technique: advances in the management of bone defects. *Int. J. Surg.* **42**, 110–116 (2017).
148. Aurégan, J.-C. & Bégué, T. Induced membrane for treatment of critical sized bone defect: a review of experimental and clinical experiences. *Int. Orthop.* **38**, 1971–1978 (2014).
149. Wang, J., Yin, Q., Gu, S., Wu, Y. & Rui, Y. Induced membrane technique in the treatment of infectious bone defect: a clinical analysis. *Orthop. Traumatol. Surg. Res.* **105**, 535–539 (2019).
150. Shen, J. et al. Treatment of infected bone defects with the induced membrane technique: a systematic review. *Bone Jt. Res.* **12**, 546–558 (2023).
151. Smink, A. M. et al. The efficacy of a prevascularized, retrievable poly(D,L,-lactide-co-ε-caprolactone) subcutaneous scaffold as transplantation site for pancreatic islets. *Transplantation* **101**, e112 (2017).
152. Patikova, A. et al. The optimal maturation of subcutaneous pouch can improve pancreatic islets engraftment in rat model. *Transplantation* **106**, 531 (2022).
153. Inoguchi, K. et al. Impact of prevascularization on immunological environment and early engraftment in subcutaneous islet transplantation. *Transplantation* **108**, 1115 (2024).
154. Sernova Corp. *A Safety, Tolerability and Efficacy Study of Sernova's Cell Pouch™ for Clinical Islet Transplantation*. https://clinicaltrials.gov/study/NCT03513939 (2025).
155. Yang, L. et al. Regenerating hair in prevascularized tissue space formed by a controllable foreign body reaction. *Adv. Funct. Mater.* **31**, 2007483 (2021).
156. Coulter, F. B. et al. Additive manufacturing of multi-scale porous soft tissue implants that encourage vascularization and tissue ingrowth. *Adv. Healthc. Mater.* **10**, 2100229 (2021).
157. Horvath, M. A. et al. Towards alternative approaches for coupling of a soft robotic sleeve to the heart. *Ann. Biomed. Eng.* **46**, 1534–1547 (2018).
158. Novosel, E. C., Kleinhans, C. & Kluger, P. J. Vascularization is the key challenge in tissue engineering. *Adv. Drug Deliv. Rev.* **63**, 300–311 (2011).
159. Hosseini, M., Brown, J. & Shafiee, A. Strategies to induce blood vessel ingrowth into skin grafts and tissue-engineered substitutes. *Tissue Eng. Part C Methods* **28**, 113–126 (2022).
160. Laschke, M. W. & Menger, M. D. Prevascularization in tissue engineering: Current concepts and future directions. *Biotechnol. Adv.* **34**, 112–121 (2016).
161. Baiguera, S. & Ribatti, D. Endothelialization approaches for viable engineered tissues. *Angiogenesis* **16**, 1–14 (2013).
162. Tsiklin, I. L., Shabunin, A. V., Kolsanov, A. V. & Volova, L. T. In vivo bone tissue engineering strategies: advances and prospects. *Polymers* **14**, 3222 (2022).
163. Laschke, M. W. et al. Improvement of vascularization of PLGA scaffolds by inosculation of in situ-preformed functional blood vessels with the host microvasculature. *Ann. Surg.* **248**, 939 (2008).
164. Kokemueller, H. et al. Prefabrication of vascularized bioartificial bone grafts in vivo for segmental mandibular reconstruction: experimental pilot study in sheep and first clinical application. *Int. J. Oral Maxillofac. Surg.* **39**, 379–387 (2010).
165. Laschke, M. W., Vollmar, B. & Menger, M. D. Inosculation: connecting the life-sustaining pipelines. *Tissue Eng. Part B Rev.* **15**, 455–465 (2009).
166. Laschke, M. W. et al. Short-term cultivation of in situ prevascularized tissue constructs accelerates inosculation of their preformed microvascular networks after implantation into the host tissue. *Tissue Eng. Part A* **17**, 841–853 (2011).
167. Laschke, M. W. et al. Promoting external inosculation of prevascularised tissue constructs by pre-cultivation in an angiogenic extracellular matrix. *Eur. Cell. Mater.* **20**, 356–366 (2010).
168. Kaempfen, A. et al. Engraftment of prevascularized, tissue engineered constructs in a novel rabbit segmental bone defect model. *Int. J. Mol. Sci.* **16**, 12616–12630 (2015).

169. Kokemüller, H. et al. En bloc prefabrication of vascularized bioartificial bone grafts in sheep and complete workflow for custom-made transplants. *Int. J. Oral Maxillofac. Surg.* **43**, 163–172 (2014).
170. Xu, J. et al. In vivo prevascularization strategy enhances neovascularization of β-tricalcium phosphate scaffolds in bone regeneration. *J. Orthop. Transl.* **37**, 143–151 (2022).
171. Zhou, X. et al. A novel animal model for skin flap prelamination with biomaterials. *Sci. Rep.* **6**, 34144 (2016).
172. Warnke, P. H. et al. Growth and transplantation of a custom vascularised bone graft in a man. *Lancet* **364**, 766–770 (2004).
173. Warnke, P. H. et al. Man as living bioreactor: fate of an exogenously prepared customized tissue-engineered mandible. *Biomaterials* **27**, 3163–3167 (2006).
174. Erol, ÖO. & Spira, M. New capillary bed formation with a surgically constructed arteriovenous fistula. *Plast. Reconstr. Surg.* **66**, 109 (1980).
175. Lokmic, Z., Stillaert, F., Morrison, W. A., Thompson, E. W. & Mitchell, G. M. An arteriovenous loop in a protected space generates a permanent, highly vascular, tissue-engineered construct. *FASEB J* **21**, 511–522 (2007).
176. Mian, R. et al. Formation of new tissue from an arteriovenous loop in the absence of added extracellular matrix. *Tissue Eng*. **6**, 595–603 (2000).
177. Izadifar, M., Kelly, M. E. & Chen, X. Engineering angiogenesis for myocardial infarction repair: recent developments, challenges, and future directions. *Cardiovasc. Eng. Technol.* **5**, 281–307 (2014).
178. Holnthoner, W., Banfi, A., Kirkpatrick, J. & Heinz, R. *Vascularization for Tissue Engineering and Regenerative Medicine* (Springer Nature, 2021).
179. Cassell, O. C. S. et al. The influence of extracellular matrix on the generation of vascularized, engineered, transplantable tissue. *Ann. N. Y. Acad. Sci.* **944**, 429–442 (2006).
180. Arkudas, A. et al. Fibrin gel-immobilized VEGF and bFGF efficiently stimulate angiogenesis in the AV loop model. *Mol. Med.* **13**, 480–487 (2007).
181. Cao, Y. et al. The influence of architecture on degradation and tissue ingrowth into three-dimensional poly(lactic-*co*-glycolic acid) scaffolds in vitro and in vivo. *Biomaterials* **27**, 2854–2864 (2006).
182. Kneser, U. et al. Engineering of vascularized transplantable bone tissues: induction of axial vascularization in an osteoconductive matrix using an arteriovenous loop. *Tissue Eng*. https://doi.org/10.1089/ten.2006.12.1721.
183. Eweida, A. M. et al. Axially vascularised mandibular constructs: Is it time for a clinical trial? *J. Cranio-Maxillofac. Surg.* **43**, 1028–1032 (2015).
184. Bitto, F. F. et al. Myogenic differentiation of mesenchymal stem cells in a newly developed neurotised AV-loop model. *BioMed Res. Int.* **2013**, 935046 (2013).
185. Beier, J. P. et al. De novo generation of axially vascularized tissue in a large animal model. *Microsurgery* **29**, 42–51 (2009).
186. Beier, J. P. et al. Axial vascularization of a large volume calcium phosphate ceramic bone substitute in the sheep AV loop model. *J. Tissue Eng. Regen. Med.* **4**, 216–223 (2010).
187. Beier, J. P. et al. De novo generation of an axially vascularized processed bovine cancellous-bone substitute in the sheep arteriovenous-loop model. *Eur. Surg. Res.* **46**, 148–155 (2011).
188. Boos, A. M. et al. Engineering axially vascularized bone in the sheep arteriovenous-loop model. *J. Tissue Eng. Regen. Med.* **7**, 654–664 (2013).
189. Weigand, A. et al. Acceleration of vascularized bone tissue-engineered constructs in a large animal model combining intrinsic and extrinsic vascularization. *Tissue Eng. Part A* https://doi.org/10.1089/ten.tea.2014.0568 (2015).
190. Eweida, A. M., Nabawi, A. S., Marei, M. K., Khalil, M. R. & Elhammady, H. A. Mandibular reconstruction using an axially vascularized tissue-engineered construct. *Ann. Surg. Innov. Res.* **5**, 2 (2011).
191. Eweida, A. M. et al. Enhancing mandibular bone regeneration and perfusion via axial vascularization of scaffolds. *Clin. Oral Investig.* **18**, 1671–1678 (2014).
192. Horch, R. E., Beier, J. P., Kneser, U. & Arkudas, A. Successful human long-term application of in situ bone tissue engineering. *J. Cell. Mol. Med.* **18**, 1478–1485 (2014).
193. Sadtler, K. et al. Design, clinical translation and immunological response of biomaterials in regenerative medicine. *Nat. Rev. Mater.* **1**, 1–17 (2016).
194. Roh, J. D. et al. Tissue-engineered vascular grafts transform into mature blood vessels via an inflammation-mediated process of vascular remodeling. *Proc. Natl. Acad. Sci. USA* **107**, 4669–4674 (2010).
195. Hibino, N. et al. A critical role for macrophages in neovessel formation and the development of stenosis in tissue-engineered vascular grafts. *FASEB J.* **25**, 4253–4263 (2011).
196. Hibino, N. et al. Tissue-engineered vascular grafts form neovessels that arise from regeneration of the adjacent blood vessel. *FASEB J.* **25**, 2731–2739 (2011).
197. Isomatsu, Y. et al. Extracardiac total cavopulmonary connection using a tissue-engineered graft. *J. Thorac. Cardiovasc. Surg.* **126**, 1958–1962 (2003).
198. Drews, J. D. et al. Spontaneous reversal of stenosis in tissue-engineered vascular grafts. *Sci. Transl. Med.* **12**, eaax6919 (2020).
199. Matsumura, G., Hibino, N., Ikada, Y., Kurosawa, H. & Shin'oka, T. Successful application of tissue engineered vascular autografts: clinical experience. *Biomaterials* **24**, 2303–2308 (2003).
200. Naito, Y. et al. Successful clinical application of tissue-engineered graft for extracardiac Fontan operation. *J. Thorac. Cardiovasc. Surg.* **125**, 419–420 (2003).
201. Breuer, T., Jimenez, M., Humphrey, J. D., Shinoka, T. & Breuer, C. K. Tissue engineering of vascular grafts: a case report from bench to bedside and back. *Arterioscler. Thromb. Vasc. Biol.* **43**, 399–409 (2023).
202. Kalaba, S. et al. Design strategies and applications of biomaterials and devices for Hernia repair. *Bioact. Mater.* **1**, 2–17 (2016).
203. Amato, G. et al. Enhanced angiogenesis in the 3D dynamic responsive implant for inguinal hernia repair ProFlor. *Artif. Organs* **45**, 933–942 (2021).
204. Hu, W. et al. Combination of polypropylene mesh and in situ injectable mussel-inspired hydrogel in laparoscopic hernia repair for preventing post-surgical adhesions in the piglet model. *ACS Biomater. Sci. Eng.* **6**, 1735–1743 (2020).
205. Zhang, P. et al. Effect of cyclic mechanical loading on immunoinflammatory microenvironment in biofabricating hydroxyapatite scaffold for bone regeneration. *Bioact. Mater.* **6**, 3097–3108 (2021).
206. Amato, G. et al. A new prosthetic implant for inguinal hernia repair: its features in a porcine experimental model. *Artif. Organs* **35**, E181–E190 (2011).
207. Amato, G. et al. Fixation free laparoscopic obliteration of inguinal hernia defects with the 3D dynamic responsive scaffold ProFlor. *Sci. Rep.* **12**, 18971 (2022).
208. Hympanova, L. et al. Physiologic musculofascial compliance following reinforcement with electrospun polycaprolactone-ureidopyrimidinone mesh in a rat model. *J. Mech. Behav. Biomed. Mater.* **74**, 349–357 (2017).
209. Lesage, F. et al. Minimal modulation of the host immune response to SIS matrix implants by mesenchymal stem cells from the amniotic fluid. *Hernia* **21**, 973–982 (2017).
210. Roman Regueros, S. et al. Acute in vivo response to an alternative implant for urogynecology. *BioMed Res. Int.* **2014**, 853610 (2014).
211. Luyten, F. P., Dell'Accio, F. & De Bari, C. Skeletal tissue engineering: opportunities and challenges. *Best Pract. Res. Clin. Rheumatol.* **15**, 759–769 (2001).

212. Li, W. et al. Subcutaneously engineered autologous extracellular matrix scaffolds with aligned microchannels for enhanced tendon regeneration: aligned microchannel scaffolds for tendon repair. *Biomaterials* **224**, 119488 (2019).
213. Lee, J. S. et al. In situ bone tissue engineering with an endogenous stem cell mobilizer and osteoinductive nanofibrous polymeric scaffolds. *Biotechnol. J.* **12**, 1700062 (2017).
214. Ding, J. et al. Bone marrow mesenchymal stem cell-based engineered cartilage ameliorates polyglycolic acid/polylactic acid scaffold-induced inflammation through M2 polarization of macrophages in a pig model. *Stem Cells Transl. Med.* **5**, 1079–1089 (2016).
215. Zhu, M. et al. In vivo engineered extracellular matrix scaffolds with instructive niches for oriented tissue regeneration. *Nat. Commun.* **10**, 4620 (2019).
216. Cohn, D., Sloutski, A., Elyashiv, A., Varma, V. B. & Ramanujan, R. In situ generated medical devices. *Adv. Healthc. Mater.* **8**, 1801066 (2019).
217. Murdock, M. H. & Badylak, S. F. Biomaterials-based in situ tissue engineering. *Curr. Opin. Biomed. Eng.* **1**, 4–7 (2017).
218. Gaharwar, A. K., Singh, I. & Khademhosseini, A. Engineered biomaterials for in situ tissue regeneration. *Nat. Rev. Mater.* **5**, 686–705 (2020).
219. Fan, Y. Bait and trap: enriching autoreactive T cells with β-cell antigen-loading biomaterial scaffolds for early detection of type 1 diabetes. *Diabetes* **66**, 2066–2068 (2017).
220. Wang, H. & Mooney, D. J. Biomaterial-assisted targeted modulation of immune cells in cancer treatment. *Nat. Mater.* **17**, 761–772 (2018).
221. Morris, A. H. et al. Engineered immunological niches to monitor disease activity and treatment efficacy in relapsing multiple sclerosis. *Nat. Commun.* **11**, 3871 (2020).
222. Rad, L. M. et al. Engineered immunological niche directs therapeutic development in models of progressive multiple sclerosis. *Proc. Natl. Acad. Sci. USA* **122**, e2409852122 (2025).
223. King, J. L. et al. Polymer scaffolds delineate healthy from diseased states at sites distal from the pancreas in two models of type 1 diabetes. *Biotechnol. Bioeng*. https://doi.org/10.1002/bit.28824 (2024).
224. Thelin, M. A. et al. In vivo enrichment of diabetogenic T cells. *Diabetes* **66**, 2220–2229 (2017).
225. Urie, R. R. et al. Biomarkers from subcutaneous engineered tissues predict acute rejection of organ allografts. *Sci. Adv*. https://doi.org/10.1126/sciadv.adk6178 (2024).
226. Bushnell, G. G. et al. Biomaterial scaffolds recruit an aggressive population of metastatic tumor cells in vivo. *Cancer Res.* **79**, 2042–2053 (2019).
227. Oakes, R. S., Froimchuk, E. & Jewell, C. M. Engineering biomaterials to direct innate immunity. *Adv. Ther.* **2**, 1800157 (2019).
228. Azarin, S. M. et al. In vivo capture and label-free detection of early metastatic cells. *Nat. Commun.* **6**, 8094 (2015).
229. Rao, S. S. et al. Enhanced survival with implantable scaffolds that capture metastatic breast cancer cells in vivo. *Cancer Res.* **76**, 5209 (2016).
230. Aguado, B. A. et al. Extracellular matrix mediators of metastatic cell colonization characterized using scaffold mimics of the pre-metastatic niche. *Acta Biomater.* **33**, 13–24 (2016).
231. Aguado, B. A. et al. Biomaterial scaffolds as pre-metastatic niche mimics systemically alter the primary tumor and tumor microenvironment. *Adv. Healthc. Mater*. https://doi.org/10.1002/adhm.201700903 (2018).
232. Oakes, R. S. et al. Metastatic conditioning of myeloid cells at a subcutaneous synthetic niche reflects disease progression and predicts therapeutic outcomes. *Cancer Res.* **80**, 602–612 (2020).
233. Morris, A. H. et al. Engineered niches to analyze mechanisms of metastasis and guide precision medicine. *Cancer Res.* **80**, 3786–3794 (2020).
234. Kemp, S. B. et al. Pancreatic cancer is marked by complement-high blood monocytes and tumor-associated macrophages. *Life Sci. Alliance* **4**, e202000935 (2021).
235. Wang, J. et al. A synthetic metastatic niche reveals antitumor neutrophils drive breast cancer metastatic dormancy in the lungs. *Nat. Commun.* **14**, 4790 (2023).
236. Raghani, R. M. et al. Engineered immunologic niche monitors checkpoint blockade response and probes mechanisms of resistance. *ImmunoMedicine* **4**, e1052 (2024).
237. Li, W. et al. Multiple comparisons of three different sources of biomaterials in the application of tumor tissue engineering in vitro and in vivo. *Int. J. Biol. Macromol.* **130**, 166–176 (2019).
238. Wolf, M. T. et al. A biologic scaffold–associated type 2 immune microenvironment inhibits tumor formation and synergizes with checkpoint immunotherapy. *Sci. Transl. Med.* **11**, eaat7973 (2019).
239. Carpenter, R. A., Kwak, J.-G., Peyton, S. R. & Lee, J. Implantable pre-metastatic niches for the study of the microenvironmental regulation of disseminated human tumour cells. *Nat. Biomed. Eng.* **2**, 915–929 (2018).
240. Zhou, Z. et al. Harnessing 3D in vitro systems to model immune responses to solid tumours: a step towards improving and creating personalized immunotherapies. *Nat. Rev. Immunol.* **24**, 18–32 (2024).
241. Gil-Moreno, A. et al. M-TRAP: safety and performance of metastatic tumor cell trap device in advanced ovarian cancer patients. *Gynecol. Oncol.* **161**, 681–686 (2021).
242. Mansouri, V. et al. Recent advances in regenerative medicine strategies for cancer treatment. *Biomed. Pharmacother.* **141**, 111875 (2021).
243. Caballero, D. et al. Precision biomaterials in cancer theranostics and modelling. *Biomaterials* **280**, 121299 (2022).
244. Aguado, B. A., Bushnell, G. G., Rao, S. S., Jeruss, J. S. & Shea, L. D. Engineering the pre-metastatic niche. *Nat. Biomed. Eng.* **1**, 1–12 (2017).
245. Najberg, M., Haji Mansor, M., Boury, F., Alvarez-Lorenzo, C. & Garcion, E. Reversing the tumor target: establishment of a tumor trap. *Front. Pharmacol*. **10**, 887 (2019).
246. Kwee, B. J. et al. Treating ischemia via recruitment of antigen-specific T cells. *Sci. Adv.* **5**, eaav6313 (2019).
247. Griffin, J. D. et al. Antigen-specific immune decoys intercept and exhaust autoimmunity to prevent disease. *Biomaterials* **222**, 119440 (2019).
248. Kim, J. et al. Injectable, spontaneously assembling, inorganic scaffolds modulate immune cells in vivo and increase vaccine efficacy. *Nat. Biotechnol.* **33**, 64–72 (2015).
249. Verbeke, C. S. & Mooney, D. J. Injectable, pore-forming hydrogels for in vivo enrichment of immature dendritic cells. *Adv. Healthc. Mater.* **4**, 2677–2687 (2015).
250. Ali, O. A., Huebsch, N., Cao, L., Dranoff, G. & Mooney, D. J. Infection-mimicking materials to program dendritic cells in situ. *Nat. Mater.* **8**, 151–158 (2009).
251. Ali, O. A., Emerich, D., Dranoff, G. & Mooney, D. J. In Situ Regulation of DC subsets and T cells mediates tumor regression in mice. *Sci. Transl. Med.* **1**, 8ra19–8ra19 (2009).
252. Roth, G. A. et al. Injectable hydrogels for sustained codelivery of subunit vaccines enhance humoral immunity. *ACS Cent. Sci.* **6**, 1800–1812 (2020).
253. Saouaf, O. M. et al. Modulation of injectable hydrogel properties for slow co-delivery of influenza subunit vaccine components enhance the potency of humoral immunity. *J. Biomed. Mater. Res. A* **109**, 2173–2186 (2021).
254. Gale, E. C. et al. Hydrogel-based slow release of a receptor-binding domain subunit vaccine elicits neutralizing antibody responses against SARS-CoV-2. *Adv. Mater.* **33**, 2104362 (2021).
255. Ou, B. S. et al. Broad and durable humoral responses following single hydrogel immunization of SARS-CoV-2 subunit vaccine. *Adv. Healthc. Mater.* **12**, 2301495 (2023).

256. Yan, J. et al. A regimen compression strategy for commercial vaccines leveraging an injectable hydrogel depot technology for sustained vaccine exposure. *Adv. Ther.* **7**, 2300108 (2024).
257. Chari, R. V. J. Targeted cancer therapy: conferring specificity to cytotoxic drugs. *Acc. Chem. Res.* **41**, 98–107 (2008).
258. Xue, L. et al. Responsive biomaterials: optimizing control of cancer immunotherapy. *Nat. Rev. Mater.* **9**, 100–118 (2024).
259. Chew, S. A. & Danti, S. Biomaterial-based implantable devices for cancer therapy. *Adv. Healthc. Mater.* **6**, 1600766 (2017).
260. Isser, A., Livingston, N. K. & Schneck, J. P. Biomaterials to enhance antigen-specific T cell expansion for cancer immunotherapy. *Biomaterials* **268**, 120584 (2021).
261. Zhang, R., Billingsley, M. M. & Mitchell, M. J. Biomaterials for vaccine-based cancer immunotherapy. *J. Controlled Release* **292**, 256–276 (2018).
262. Ruan, S., Huang, Y., He, M. & Gao, H. Advanced biomaterials for cell-specific modulation and restore of cancer immunotherapy. *Adv. Sci.* **9**, 2200027 (2022).
263. Cheung, A. S., Zhang, D. K. Y., Koshy, S. T. & Mooney, D. J. Scaffolds that mimic antigen-presenting cells enable ex vivo expansion of primary T cells. *Nat. Biotechnol.* **36**, 160–169 (2018).
264. Ren, L. & Lim, Y. T. Degradation-regulatable architectured implantable macroporous scaffold for the spatiotemporal modulation of immunosuppressive microenvironment and enhanced combination cancer immunotherapy. *Adv. Funct. Mater.* **28**, 1804490 (2018).
265. Brudno, Y. et al. Replenishable drug depot to combat post-resection cancer recurrence. *Biomaterials* **178**, 373–382 (2018).
266. Sun, M. et al. A tissue-engineered therapeutic device inhibits tumor growth in vitro and in vivo. *Acta Biomater* **18**, 21–29 (2015).
267. Adu-Berchie, K. & Mooney, D. J. Biomaterials as local niches for immunomodulation. *Acc. Chem. Res.* **53**, 1749–1760 (2020).
268. Kharbikar, B. N., Chendke, G. S. & Desai, T. A. Modulating the foreign body response of implants for diabetes treatment. *Adv. Drug Deliv. Rev.* **174**, 87–113 (2021).
269. Christou, C., Oliver, R. A., Yu, Y. & Walsh, W. R. The masquelet technique for membrane induction and the healing of ovine critical sized segmental defects. *PLoS One* **9**, e114122 (2014).
270. Sarah, J. *Masquelet Technique* https://app.biorender.com/biorender-templates/details/t-63dd838c54ec321a0a15b040-masquelet-technique/?source=gallery (2025).

Acknowledgements

This work was supported in part by NIH Pathway to Independence Award R00EB028840 to A.H.M. and by United States Department of Veterans Affairs Career Development Award IK2BX005061 to R.S.O. This work was additionally supported by the NIH Tissue Engineering and Regeneration Training Grant under Grant No. DE007057 to M.E.D. and the NSF Graduate Research Fellowship under Grant No. DGE 2241144 to M.E.D. Any opinions, findings, and conclusions or recommendations expressed in this material are those of the authors and do not necessarily reflect the views of the NIH, Department of Veterans Affairs, United States Government, or NSF.

Author contributions

R.S.O. and A.H.M. conceptualized the article idea. M.E.D., R.S.O., and A.H.M. performed the literature search. M.E.D. wrote the manuscript and designed the original table and figures with support from R.S.O. and A.H.M. M.E.D., R.S.O., and A.H.M. edited the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

Correspondence and requests for materials should be addressed to Aaron H. Morris.