Review

Not peer-reviewed version

Soft Tissue Scaffolds in Breast Reconstruction: Evolution from Acellular Dermal Matrices to Synthetic Polymers

Rebecca Lisk , Thomas J. Sorenson * , Carter J. Boyd , Nolan S. Karp

Posted Date: 24 March 2026

doi: 10.20944/preprints202603.1941.v1

Keywords: soft tissue support; breast reconstruction; acellular dermal matrix; mesh; scaffolds; bioresorbable

 doi:10.20944/preprints202603.1941.v1

Review

Soft Tissue Scaffolds in Breast Reconstruction: Evolution from Acellular Dermal Matrices to Synthetic Polymers

Rebecca Lisk, Thomas J Sorenson, Carter J Boyd and Nolan S. Karp

Hansjorg Wyss Department of Plastic Surgery, NYU-Langone Health, 222 E 41st Street, New York, NY

* Correspondence: thomas.sorenson@nyulangone.org

Abstract

Soft tissue reconstruction often requires biomaterials that provide temporary mechanical support while allowing vascular integration and tissue remodeling. In reconstructive breast surgery, these demands converge within a uniquely challenging environment characterized by large surface areas, variable perfusion, frequent exposure to radiation, and reliance on prosthetic implants. As a result, breast reconstruction has emerged as a clinically relevant model for evaluating the performance and limitations of soft tissue scaffolds. Acellular dermal matrices (ADM) were initially adopted to provide biologically derived reinforcement based on the premise of host integration and neovascularization. While ADM reshaped implant-based reconstruction, accumulating clinical experience has revealed important constraints, including variability in mechanical properties, inconsistent vascularization, susceptibility to fibrosis, and limited performance in compromised tissue beds. These limitations have driven increasing interest in synthetic polymer scaffolds engineered for predictable mechanics, controlled degradation, and scalable manufacturing. This narrative review examines the evolution from ADM to synthetic and hybrid scaffold systems in breast reconstruction. We discuss how scaffold architecture, thickness, porosity, and degradation kinetics influence angiogenesis, immune response, and mechanical load transfer during healing. Hybrid strategies that integrate selective bioactivity within synthetic frameworks are also considered, highlighting both their translational promise and practical challenges. These concepts are particularly relevant for implant-based breast reconstruction, where scaffold performance directly influences complication rates, implant stability, and long-term reconstructive outcomes.

Keywords: soft tissue support; breast reconstruction; acellular dermal matrix; mesh; scaffolds; bioresorbable

1. Introduction

Soft tissue reconstruction often requires coordinated restoration of volume, mechanical support, vascular perfusion, and tissue architecture. In reconstructive breast surgery, these demands converge within a uniquely challenging biological environment characterized by large surface areas, tenuous perfusion, frequent exposure to radiation, and the presence of prosthetic implants [1–3]. As a result, breast reconstruction has emerged as a clinically relevant testing ground for biomaterial-based soft tissue support strategies.

Over the past two decades, acellular dermal matrices (ADM) have played a central role in reshaping implant-based breast reconstruction by providing immediate structural support and a biologically derived scaffold for tissue incorporation [4–8]. Their rapid clinical adoption was driven by the promise of host integration, neovascularization, and remodeling into native-like tissue [9,10]. However, accumulating clinical experience has revealed important limitations related to variability, cost, inflammatory response, and inconsistent vascularization, particularly in compromised tissue beds [4,11–17]. Additionally, all use of soft tissue support in the breast is not United States Food and

 doi:10.20944/preprints202603.1941.v1

Drug Administration (FDA) approved, making it challenging to construct studies for evaluation of true clinical outcomes [18].

These challenges have catalyzed growing interest in synthetic polymer scaffolds designed to provide predictable mechanical performance, controlled degradation, and scalable manufacturing [19–22]. Unlike biologic matrices, synthetic materials can be engineered with defined microarchitecture, degradation kinetics, and mechanical properties tailored to the demands of soft tissue support [23,24]. This narrative review examines the evolution from ADM to synthetic polymers in breast surgery, using this clinical domain to extract broader design principles relevant to soft tissue reconstruction and repair. An overview of these materials is found in Table 1.

Table 1. Representative Soft Tissue Scaffolds Used in Breast Reconstruction.

Scaffold Category	Representative Materials	Commercial Examples	Key Design Features	Advantages	Limitations
Acellular Dermal Matrices (ADM)	Decellularized human or animal dermis retaining extracellular matrix proteins (collagen, elastin, structural ECM)	AlloDerm®, DermACELL®, FlexHD®, SurgiMend®, Strattice®	Biologic scaffold intended to support host cell infiltration and neovascularization	• Biologic integration • Good handling characteristics • Extensive clinical experience	• Batch variability • High cost • Inconsistent vascularization • Risk of inflammatory response or fibrosis
Synthetic Permanent Meshes	Non-resorbable polymers (e.g., polypropylene, polyester)	Prolene® mesh, Parietex® mesh	Durable polymer mesh providing long-term mechanical reinforcement	• Strong mechanical support • Low material variability	• Chronic foreign body response • Stiffness mismatch • Long-term complications • Limited use in contemporary breast reconstruction
Synthetic Resorbable Scaffolds	Bioabsorbable polymers designed to degrade over time (e.g.,	GalaFLEX® (P4HB), TIGR® Matrix, Vicryl® mesh	Temporary load-sharing scaffold that gradually transfers	• Predictable mechanical properties • Controlled degradation	• Limited bioactivity • Dependence on host vascularization

 doi:10.20944/preprints202603.1941.v1

	poly-4-hydroxybutyrate, polylactic acid, polyglactin)		mechanical support to host tissue	• Lower long-term foreign body burden	• Long-term outcome data still evolving
Hybrid / Composite Scaffolds	Combination of synthetic polymers with biologic components or biofunctionalized surfaces	P4HB with ECM coatings (experimental), collagen-polymer composites, biofunctionalized electrospun scaffolds	Integrate mechanical reliability of synthetic materials with selective biologic signaling	• Potential for improved angiogenesis • Potential for improved immune modulation • Tunable architecture	• Increased manufacturing complexity • Regulatory challenges • Limited clinical adoption to date

key: ECM extracellular matrix, P4HB poly-4-hydroxybutyrate, ADM acellular dermal matrix.

2. Acellular Dermal Matrices: Origin and Early Success

Acellular dermal matrices were introduced into reconstructive surgery as a means of harnessing the instructive properties of native extracellular matrix (ECM) while minimizing immunogenicity[25,26]. Derived from human or animal dermis through decellularization processes, ADMs retain key structural proteins such as collagen and elastin, as well as bioactive cues thought to support cell migration, angiogenesis, and tissue remodeling [27–29].

In breast reconstruction, ADMs were rapidly adopted to reinforce the implant pocket, define the inframammary fold, and facilitate immediate reconstruction following mastectomy [4,30,31]. Early clinical experience suggested benefits including improved implant positioning, reduced capsular contracture, and enhanced soft tissue coverage [30,32,33]. These advantages were attributed to the biologic integration of ADM into host tissue, with neovascularization enabling long-term incorporation [6].

From a bioengineering perspective, ADMs offered an appealing paradigm: a naturally derived scaffold with inherent bioactivity capable of supporting vascular ingrowth without the need for exogenous growth factors or cells [6]. Their success accelerated broader interest in decellularized matrices across soft tissue repair applications, including abdominal wall reconstruction, extremity coverage, and pelvic floor repair [34–36].

3. Limitations of Acellular Dermal Matrices in Clinical Practice

Despite their widespread adoption, acellular dermal matrices exhibit several limitations that have become increasingly apparent with expanded clinical use and longer-term follow-up. Many of these constraints arise from the inherent variability of biologically derived materials and from a mismatch between the biological assumptions underlying ADM use and the mechanical and vascular realities of reconstructive breast surgery.

3.1. Variability in Source, Processing, and Mechanical Properties

ADMs are derived from human or animal dermis and undergo multistep decellularization, sterilization, and preservation processes that vary substantially between manufacturers [29,37,38].

 doi:10.20944/preprints202603.1941.v1

These differences affect collagen architecture, residual bioactive components, thickness, stiffness, and tensile strength [13,14,28,37,38]. As a result, ADM products are not mechanically equivalent, and even within a single product line, batch-to-batch variability may occur [28]. From an engineering standpoint, this lack of reproducibility complicates reliable load sharing and limits precise matching of scaffold mechanics to the evolving demands of healing soft tissue [12].

3.2. Inconsistent Vascularization and Host Integration

The clinical utility of ADM relies heavily on timely neovascularization to support incorporation and long-term function. However, vascular ingrowth into ADM is highly dependent on local tissue conditions, including perfusion of mastectomy flaps, prior radiation, and the presence of implants [4,6,11]. In thicker matrices or compromised tissue beds, diffusion limitations and delayed angiogenesis may lead to partial incorporation, persistent acellularity, or chronic inflammatory response [4,11,39,40]. These phenomena challenge the assumption that biologic origin alone guarantees effective vascular integration.

3.3. Fibrosis, Inflammation, and Encapsulation

While ADMs are designed to reduce immunogenicity, they are not immunologically inert. Persistent foreign body response, fibroblast activation, and macrophage-mediated inflammation have been observed in both experimental and clinical settings [17,41]. In some cases, this response manifests as excessive fibrosis, thickening of the reconstructed pocket, or a contribution to capsular contracture [16]. Importantly, these outcomes undermine one of the primary theoretical advantages of ADM, which is facilitation of organized, regenerative tissue remodeling rather than fibrosis-dominated scarring.

3.4. Performance in Irradiated and Revision Settings

Radiation therapy remains one of the most significant challenges in breast reconstruction due to its deleterious effects on vascular density, fibroblast behavior, and tissue compliance [42–45]. In irradiated fields, ADM incorporation is frequently delayed or incomplete, and complication rates, including infection, seroma, and reconstructive failure, are increased [11,46,47]. Similar vulnerabilities are observed in revision surgery, where prior scarring and altered vascular anatomy further limit the biologic potential of decellularized matrices [1,48].

3.5. Implications for Scaffold Design Evolution

Collectively, these limitations highlight a fundamental tension between biologic mimicry and engineering predictability. While ADMs do offer valuable bioactive cues, their variability, dependence on host vascular conditions, and inconsistent mechanical behavior limit their reliability as universal soft tissue support solutions [12,15]. These shortcomings have driven growing interest in synthetic polymer scaffolds engineered to deliver controlled mechanical support, predictable degradation, and reproducible integration across a broader range of clinical scenarios [49,50].

4. Emergence of Synthetic Polymer Scaffolds for Soft Tissue Support

The limitations of acellular dermal matrices have prompted a paradigm shift toward synthetic polymer–based scaffolds engineered to provide predictable mechanical support, controlled degradation, and scalable manufacturing [49,50]. Rather than attempting to recapitulate the full biological complexity of native extracellular matrix, synthetic scaffolds are designed around principles of soft tissue repair, that is: temporary load sharing during the initial wound healing phase, followed by gradual transfer of mechanical load to vascularized host tissue [21,51]. In breast surgery, resorbable synthetic scaffolds such as poly-4-hydroxybutyrate (P4HB), Vicryl mesh, and other biosynthetic matrices have been increasingly adopted to provide temporary soft tissue reinforcement while avoiding the long-term persistence of permanent polymers[52-54].

 doi:10.20944/preprints202603.1941.v1

4.1. Mechanical Load Sharing

One of the primary advantages of synthetic polymer scaffolds is the ability to define and reproduce mechanical performance parameters such as tensile strength, elasticity, and creep resistance [19,22,55]. In breast reconstruction, these properties influence implant positioning, contour stability, and resistance to deformation under gravitational and muscular forces [55]. Importantly, synthetic scaffolds can be designed to distribute mechanical loads across a broader surface area, reducing focal stress on fragile mastectomy flaps or compromised tissues [56]. This load-sharing function is especially critical in the early postoperative period, when vascular supply is still evolving and tissue tolerance to strain is limited [57].

4.2. Host Response and Integration

Unlike biologic matrices, synthetic polymers do not inherently contain bioactive cues. Rather, their integration depends on host-mediated cellular infiltration and neovascularization, and scaffold architecture plays a central role in facilitating this process [58,59]. Properly designed synthetic scaffolds can support fibroblast migration, endothelial ingrowth, and gradual tissue incorporation without excessive fibrosis [59–61]. The host response to resorbable polymers is also influenced by degradation byproducts, which must be biocompatible and metabolically managed [62,63]. When degradation kinetics are appropriately matched to tissue healing rates, inflammatory responses are ideally transient rather than chronic, which supports constructive remodeling rather than encapsulation [60,64].

4.3. Predictability as Design Motivation

Synthetic polymers offer a level of reproducibility that is difficult to achieve with biologic materials. Polymer chemistry, molecular weight, crystallinity, and processing methods can be precisely controlled, enabling consistent mechanical properties and degradation behavior across batches [65]. This predictability is particularly valuable in breast reconstruction, where scaffold performance must be reliable across patients with widely variable tissue quality, perfusion, and exposure to adjuvant therapies. From an engineering perspective, the goal of synthetic soft tissue scaffolds is not permanent replacement of native tissue, but rather temporary mechanical reinforcement during a biologically vulnerable period [66,67]. By providing early structural support and then resorbing as host tissue remodels, these materials aim to reduce stress concentrations, limit tissue deformation, and promote organized healing [50,60,68].

4.4. Resorbable Versus Permanent Polymers

Early generations of synthetic meshes relied on permanent polymers that offered durable strength but were associated with chronic foreign body response, stiffness mismatch, and long-term complications [69]. In contrast, contemporary soft tissue applications increasingly favor resorbable polymers, which are engineered to degrade over months to years in parallel with tissue maturation [66,69,70]. These resorbable scaffolds can be designed particularly so that loss of mechanical integrity coincides with the development of sufficient host tissue strength and vascularization [66,70,71]. This time-dependent design distinguishes modern synthetic approaches from both permanent meshes and biologic matrices, offering a more deliberate alignment between material behavior and wound healing biology [66,70].

5. Hybrid and Composite Scaffold Strategies for Breast Soft Tissue Support

As experience with both biologic and synthetic scaffolds has matured, it has become increasingly clear that neither approach alone fully addresses the complex demands of soft tissue reconstruction. This recognition has driven the development of hybrid and composite scaffolds that seek to combine the biological signaling advantages of extracellular matrix–derived materials with the mechanical predictability and scalability of synthetic polymers [72,73].

 doi:10.20944/preprints202603.1941.v1

5.1. Rationale for Hybrid Scaffolds

Hybrid scaffolds are motivated by the observation that biologic matrices excel at providing cell-adhesive cues and promoting angiogenesis, while synthetic polymers offer superior control over mechanical behavior, degradation kinetics, and manufacturing consistency [74,75]. By integrating these complementary features, composite systems aim to support early vascularization and tissue integration without sacrificing structural reliability [75]. In breast reconstruction, where scaffolds must function in mechanically loaded, perfusion-limited environments, hybrid strategies offer a theoretical advantage. The goal is not to recreate native tissue wholesale, but to engineer a scaffold that delivers selective bioactivity while maintaining a defined mechanical role during healing [73].

Hybrid scaffold designs span a range of strategies from simple physical composites to more sophisticated biofunctionalized polymers. One approach involves combining a synthetic structural backbone with a biologic surface or coating derived from decellularized matrix components [76]. This configuration preserves bulk mechanical integrity while presenting bioactive cues that facilitate cell attachment and angiogenesis at the tissue–scaffold interface [76]. Another strategy employs biofunctionalization of synthetic polymers, incorporating short peptide sequences, growth factor–binding domains, or extracellular matrix fragments to modulate host response [77–80]. These modifications can influence macrophage polarization, fibroblast behavior, and endothelial migration without introducing the variability associated with whole-tissue biologics [77–80].

5.2. Hybrid Scaffold Architecture

Beyond material composition, hybrid scaffolds leverage architectural design to enhance vascular integration. Controlled pore size, fiber alignment, and spatial patterning can direct cell infiltration and capillary formation [81–83]. In this context, biologic cues function synergistically with physical architecture, reinforcing angiogenic pathways that are already favored by scaffold geometry [83]. For breast soft tissue support, where diffusion distances and tissue thickness are critical constraints, hybrid scaffolds may enable more efficient vascular penetration while maintaining thin, load-sharing constructs [20,84]. This architectural–biological coupling represents a key advance over earlier scaffold designs that relied primarily on material composition alone.

5.3. Immunomodulation and Remodeling

An emerging focus of hybrid scaffold development is immunomodulation rather than simple immune avoidance. By shaping the early inflammatory milieu, hybrid materials can promote constructive remodeling rather than fibrotic encapsulation [77,85–87]. Selective presentation of bioactive signals within a synthetic framework allows for targeted immune engagement without the prolonged inflammatory responses sometimes associated with biologic matrices [77,85–87]. This immunologically informed design approach is especially relevant in breast reconstruction, where chronic inflammation can contribute to capsular contracture, contour irregularities, and reconstructive failure [88].

5.4. Challenges and Limitations

Despite their conceptual appeal, hybrid scaffolds introduce additional complexity in manufacturing, regulatory approval, and clinical deployment [21,89,90]. Combining biologic and synthetic components increases variability, complicates sterilization, and may reintroduce supply chain dependencies [89–91]. Furthermore, isolating the clinical benefit of added bioactivity can be challenging, particularly when surgical technique and host factors exert strong influence over outcomes [92]. These considerations underscore the need for indication-specific hybridization, rather than broad application of biologic augmentation. In some clinical scenarios, purely synthetic scaffolds may suffice, whereas in others, targeted biologic signaling may offer incremental benefit [21,76].

 doi:10.20944/preprints202603.1941.v1

6. Design Constraints for Soft Tissue Support

Across all soft tissue reconstruction strategies, vascularization remains the principal biological determinant of scaffold success [93–95]. Regardless of material composition, mechanical strength, or bioactivity, scaffolds that fail to support timely perfusion are predisposed to inflammation, fibrosis, infection, and structural failure [93]. Breast reconstruction highlights this reality particularly clearly as scaffolds are routinely implanted into tissue beds with compromised vascularity due to mastectomy, prior surgery, or radiation therapy [3].

6.1. Diffusion Limits on Scaffold Thickness

Oxygen and nutrient diffusion impose strict physical limits on scaffold design. In the absence of intrinsic vasculature, cell survival within implanted scaffolds depends on diffusion from adjacent tissues until angiogenesis occurs [96]. Excessive scaffold thickness or dense microarchitecture increases diffusion distances, delaying vascular penetration and creating hypoxic regions vulnerable to necrosis and chronic inflammation [96–98]. These constraints are especially relevant in breast reconstruction, where scaffolds often span large surface areas and interface with thin, occasionally poorly perfused, mastectomy flaps [76].

Most clinically deployed soft tissue scaffolds rely on angiogenesis with capillary sprouting from existing host vessels [99]. While effective in well-perfused tissues, angiogenesis proceeds more slowly in irradiated or scarred environments [76]. Vasculogenesis offers theoretical advantages but remains challenging to achieve in clinical scaffolds without exogenous cellular or molecular augmentation [100,101]. Synthetic and hybrid scaffold designs increasingly recognize this limitation, emphasizing permissive architecture and degradation rather than attempting to force vascularization through biologic signaling alone [82,102]. This pragmatic approach aligns scaffold function with realistic expectations of host vascular capacity.

6.2. Scaffold Architecture and Vascularization

Microarchitectural features such as pore size, interconnectivity, and fiber alignment exert a strong influence over vascular ingrowth [102–104]. Larger, interconnected pores facilitate endothelial migration and capillary looping, while anisotropic fiber orientation can guide vessel directionality [104]. These architectural parameters often have a greater impact on vascularization than material chemistry alone [102,104]. In breast reconstruction, thin, macroporous scaffolds are favored to minimize diffusion barriers and encourage uniform perfusion [20,97]. Hybrid scaffolds that combine architectural guidance with selective bioactivity may further enhance vascular efficiency without increasing scaffold bulk [105].

6.3. Balancing the Timing of Vascularization with Mechanical Support

An underappreciated design challenge is the need to synchronize vascular integration with mechanical load sharing [19,51]. Scaffolds must maintain sufficient strength during the period of limited perfusion while avoiding prolonged persistence that could perpetuate inflammation once vascularization is established [60,71]. Resorbable synthetic polymers are particularly well suited to this temporal coupling, as their degradation profiles can be engineered to align with the progression of angiogenesis and tissue remodeling [20,60,71,106].

6.4. Implications for Future Scaffold Design

The experience of breast reconstruction suggests that vascularization should be treated not as a secondary outcome, but as a primary design constraint [93]. Successful soft tissue scaffolds must be thin, porous, and mechanically supportive while remaining permissive to host-driven vascular integration [19,20,104]. Advances in biofabrication, including spatial patterning and gradient architectures, offer promising avenues to further optimize this balance [19,20,107,108].

 doi:10.20944/preprints202603.1941.v1

7. Translational Lessons from Breast Reconstruction for Soft Tissue Repair

Breast reconstruction offers a uniquely informative translational model for evaluating soft tissue scaffolds, as it combines high mechanical demand, variable vascularity, frequent use of foreign materials, and long-term functional and aesthetic endpoints [21,76]. Lessons drawn from this field extend beyond breast surgery, informing biomaterial design across diverse soft tissue reconstruction applications [109].

7.1. Clinical Context Shapes Biomaterial Performance

One of the clearest lessons from breast reconstruction is that biomaterial performance is inseparable from the surgical context. Tissue perfusion, flap thickness, radiation exposure, and surgical technique exert effects that may overshadow intrinsic material properties [46,57,110]. As a result, scaffolds that perform well in preclinical models or select clinical scenarios may fail when applied indiscriminately [46,111]. This reality argues against one-size-fits-all biomaterial solutions and supports context-specific scaffold selection based on tissue quality and reconstructive goals.

7.2. Engineering Reliability Versus Biological Naturality

The historical progression from ADM to synthetic polymers reflects a broader shift away from biological idealism toward engineering reliability. While biologic matrices offer theoretical advantages in bioactivity, their dependence on host vascular capacity and inherent variability limit reproducibility [111,112]. Synthetic scaffolds, by contrast, prioritize consistent mechanical behavior and controlled interaction with host biology [113]. Breast reconstruction demonstrates that predictability and controlled degradation can be as clinically valuable as biologic mimicry, particularly in hostile tissue environments [47,68,113].

7.3. Surgical Technique Is a Determinant of Scaffold Success

Scaffold performance cannot be fully separated from surgical handling, fixation, and placement. Tension distribution, scaffold orientation, and interface with native tissue all influence mechanical load transfer and vascular access [56,93,114,115]. Breast reconstruction highlights the importance of surgeon–engineer alignment, where material design anticipates real-world surgical use rather than idealized deployment conditions. Complications such as infection, seroma, capsular contracture, and reconstructive failure provide critical feedback for scaffold design [116–120]. These failure modes often reflect mismatches between scaffold properties and tissue biology, including excessive stiffness, delayed resorption, or inadequate vascular integration [51,115]. Incorporating clinical failure data into iterative design cycles is essential for advancing soft tissue scaffold technology [121].

7.4. Broader Implications for Soft Tissue Reconstruction

The evolution of scaffold use in breast reconstruction illustrates a generalizable framework for soft tissue repair: prioritize vascular permissiveness, match mechanical support to healing timelines, and design for reproducibility and scalability [20,21,89,93]. These principles apply across reconstructive contexts, from abdominal wall repair to extremity reconstruction and beyond [40,81]. By serving as a clinically demanding testbed, breast reconstruction continues to inform the development of next-generation biomaterials that integrate engineering precision with biological realism [109].

8. Future Directions in Soft Tissue Scaffold Design

Continued progress in soft tissue reconstruction will depend on scaffold strategies that integrate vascular permissiveness, mechanical reliability, and immunologic control while remaining practical for surgical translation [64,82,93,122,123]. Insights gained from the evolution of scaffold use in breast reconstruction suggest several priority directions for future biomaterial development.

 doi:10.20944/preprints202603.1941.v1

8.1. Vascular-Patterned and Gradient Scaffolds

One promising avenue is the incorporation of spatially defined architectures that actively guide vascular ingrowth [108,124–127]. Advances in biofabrication, including additive manufacturing and controlled fiber deposition, enable the creation of scaffolds with gradient porosity, anisotropic mechanics, and preferential vascular pathways [128–131]. Such designs may better accommodate diffusion limits while preserving load-sharing capacity, particularly in large or perfusion-limited soft tissue reconstructions [108,132]. Rather than relying solely on biochemical cues, these approaches emphasize physical guidance of angiogenesis, aligning scaffold geometry with known principles of vessel formation and remodeling.

8.2. Immunomodulatory Material Design

Future scaffolds are likely to move beyond passive biocompatibility toward active modulation of the host immune response [123,133]. Early inflammatory signaling plays a decisive role in determining whether healing proceeds toward regenerative remodeling or fibrotic encapsulation [123]. Synthetic and hybrid scaffolds that bias macrophage polarization and fibroblast behavior toward constructive pathways may reduce long-term complications such as fibrosis and contracture [77,78,123]. Importantly, immunomodulation must be tightly controlled and indication-specific to avoid unintended systemic or chronic effects [134].

8.3. Personalized and Context-Specific Scaffold Selection

As understanding of tissue-specific biology improves, scaffold selection is likely to become more personalized, accounting for factors such as prior radiation, tissue thickness, vascular status, and reconstructive goals [93,111,115,135]. Rather than a single “best” scaffold, future practice may involve algorithmic or decision-guided material selection, matching scaffold properties to patient-specific risk profiles [136,137]. Breast reconstruction, with its heterogeneity of clinical scenarios, provides a natural framework for developing and validating such precision approaches.

8.4. Minimally Invasive and Injectable Strategies

Injectable and minimally invasive scaffold systems represent an emerging frontier in soft tissue support [138]. These approaches aim to reduce surgical trauma while providing localized mechanical reinforcement and biological modulation [138]. While challenges remain in achieving sufficient mechanical strength and spatial control, advances in shear-thinning hydrogels and in situ polymerization may expand the applicability of these systems [139–141].

8.5. Translational Integration

Finally, future success will depend on tighter integration between material scientists, surgeons, and clinical researchers. Iterative design informed by real-world failure modes will be essential [121,142]. Breast reconstruction offers a valuable feedback-rich environment for this process, accelerating translation from bench to bedside.

9. Conclusions

The evolution of soft tissue scaffolds in breast reconstruction from acellular dermal matrices to synthetic polymers and hybrid systems reflects a broader maturation of biomaterial design philosophy. Early reliance on biologic mimicry has given way to a more pragmatic emphasis on engineering predictability, vascular permissiveness, and controlled host interaction. Clinical experience has demonstrated that successful soft tissue support depends less on material origin than on alignment between scaffold properties and the biological and mechanical realities of the reconstructive environment. Breast reconstruction, with its high demands and frequent vascular compromise, serves as a stringent translational model for evaluating these principles. As the field

 doi:10.20944/preprints202603.1941.v1

advances, future scaffold strategies will need to prioritize vascular integration as a primary design constraint and couple mechanical support to healing timelines, while accommodating changing and imperfect patient-specific tissue conditions.

Author Contributions: TJS, RL, CB contributed to the conceptualization, literature search, and writing of the manuscript. NK contributed to the conceptualization, and critical review and editing of the manuscript. All authors approved the final manuscript.

Funding: The authors have no funding sources to report.

Institutional Review Board Statement: Not applicable.

Acknowledgments: The authors have no acknowledgments related to this paper to report.

Conflicts of Interest: The authors have no financial conflicts of interest related to this paper to report.

References

1. Sorenson TJ, Boyd CJ, Cohen O, Choi M, Karp N. Microsurgical Strategies in Post-Radiation and Revision Breast Reconstruction: Optimizing Outcomes in High-Risk Patients. *Cancers (Basel)*. Nov 29 2025;17(23)doi:10.3390/cancers17233831
2. Friedrich M, Kramer S, Friedrich D, Kraft C, Maass N, Rogmans C. Difficulties of Breast Reconstruction - Problems That No One Likes to Face. *Anticancer Res*. Nov 2021;41(11):5365-5375. https://doi.org/10.21873/anticanres.15349
3. Thiruchelvam PTR, Leff DR, Godden AR, et al. Primary radiotherapy and deep inferior epigastric perforator flap reconstruction for patients with breast cancer (PRADA): a multicentre, prospective, non-randomised, feasibility study. *Lancet Oncol*. May 2022;23(5):682-690. https://doi.org/10.1016/S1470-2045(22)00145-0
4. Dikmans RE, Negenborn VL, Bouman MB, et al. Two-stage implant-based breast reconstruction compared with immediate one-stage implant-based breast reconstruction augmented with an acellular dermal matrix: an open-label, phase 4, multicentre, randomised, controlled trial. *Lancet Oncol*. Feb 2017;18(2):251-258. https://doi.org/10.1016/S1470-2045(16)30668-4
5. Woussen A, Pluvy I, Maisonnette Y, Chaput B, Ferreira D, Feuvrier D. Interest of acellular dermal matrices in immediate breast reconstruction: Comparison of quality of life and complications with and without matrix. *J Plast Reconstr Aesthet Surg*. Nov 2023;86:128-138. https://doi.org/10.1016/j.bjps.2023.08.007
6. du Plessis MI, Cottler PS, Campbell CA. Acellular Dermal Matrix Favorably Modulates the Healing Response after Surgery. *Plast Reconstr Surg*. Aug 1 2022;150(2):290e-299e. https://doi.org/10.1097/PRS.0000000000009338
7. Amro C, Sorenson TJ, Boyd CJ, et al. The Evolution of Implant-Based Breast Reconstruction: Innovations, Trends, and Future Directions. *J Clin Med*. Dec 05 2024;13(23)doi:10.3390/jcm13237407
8. Sorenson TJ, Boyd CJ, Karp NS. Hot Topics in Implant-Based Breast Reconstruction. *J Clin Med*. Dec 29 2025;15(1)doi:10.3390/jcm15010263
9. Salzberg CA. Nonexpansive immediate breast reconstruction using human acellular tissue matrix graft (AlloDerm). *Ann Plast Surg*. Jul 2006;57(1):1-5. https://doi.org/10.1097/01.sap.0000214873.13102.9f
10. Gamboa-Bobadilla GM. Implant breast reconstruction using acellular dermal matrix. *Ann Plast Surg*. Jan 2006;56(1):22-5. https://doi.org/10.1097/01.sap.0000185460.31188.c1
11. Mendenhall SD, Graham EM, Anderson LA, Ying J, Liu T, Agarwal JP. Impact of Chemotherapy and Radiation Therapy on Inflammatory Response, Neovascularization, and Capsule Formation of Acellular Dermal Matrix in Breast Reconstruction: Analysis of the BREASTrial Biopsy Specimens. *Plast Reconstr Surg*. Mar 1 2022;149(3):378e-385e. https://doi.org/10.1097/PRS.0000000000008824
12. Stec E, Lombardi J, Augustin J, Sandor M. Acellular Dermal Matrix Susceptibility to Collagen Digestion: Effect on Mechanics and Host Response. *Tissue Eng Part A*. May 2023;29(9-10):269-281. https://doi.org/10.1089/ten.TEA.2022.0155

 doi:10.20944/preprints202603.1941.v1

13. Nilsen TJ, Dasgupta A, Huang YC, Wilson H, Chnari E. Do Processing Methods Make a Difference in Acellular Dermal Matrix Properties? *Aesthet Surg J*. Nov 2016;36(suppl 2):S7-S22. https://doi.org/10.1093/asj/sjw163
14. Kollmetz T, Castillo-Alcala F, Veale RWF, et al. Comparative Analysis of Commercially Available Extracellular Matrix Soft Tissue Bioscaffolds. *Tissue Eng Part A*. Jun 2025;31(11-12):442-455. https://doi.org/10.1089/ten.TEA.2024.0076
15. DeGeorge BR, Jr., Olenczak JB, Cottler PS, et al. Evaluation of Sidestream Darkfield Microscopy for Real-Time Imaging Acellular Dermal Matrix Revascularization. *Ann Plast Surg*. Jun 2016;76 Suppl 4:S255-9. https://doi.org/10.1097/SAP.0000000000000832
16. Kearney AM, Yan Y, Bricker JT, Pincus JL, Alghoul MS. Acellular Dermal Matrix-Associated Contracture: A Clinical and Histologic Analysis of Patients Undergoing Prosthetic Breast Reconstruction. *Plast Reconstr Surg*. Nov 1 2021;148(5):968-977. https://doi.org/10.1097/PRS.0000000000008485
17. Lee JH, Choi BG, Lee WS, et al. Long-Term Ultrasonographic and Histologic Changes in Acellular Dermal Matrix in Implant-Based Breast Reconstructions. *Plast Reconstr Surg*. Sep 1 2023;152(3):514-522. https://doi.org/10.1097/PRS.0000000000010321
18. Boyd CJ, Bekisz JM, Choi M, Karp NS. Catch-22: Acellular Dermal Matrix and U.S. Food and Drug Administration Premarket Approval-How Can We Construct Studies? *Plast Reconstr Surg*. Dec 01 2022;150(6):1363-1366. https://doi.org/10.1097/PRS.0000000000009701
19. Zhou M, Hou J, Zhang G, et al. Tuning the mechanics of 3D-printed scaffolds by crystal lattice-like structural design for breast tissue engineering. *Biofabrication*. Dec 31 2019;12(1):015023. https://doi.org/10.1088/1758-5090/ab52ea
20. Kracoff-Sella S, Goldfracht I, Silverstein A, et al. Rational design of 3D-printed scaffolds for breast tissue engineering using structural analysis. *Biofabrication*. Feb 17 2025;17(2)doi:10.1088/1758-5090/adaf5a
21. De Sario Velasquez GD, Tanas Y, Taraballi F, Herzog T, Spiegel A. State of Research on Tissue Engineering with 3D Printing for Breast Reconstruction. *J Clin Med*. Sep 24 2025;14(19)doi:10.3390/jcm14196737
22. Hoque ME. Robust formulation for the design of tissue engineering scaffolds: A comprehensive study on structural anisotropy, viscoelasticity and degradation of 3D scaffolds fabricated with customized desktop robot based rapid prototyping (DRBRP) system. *Mater Sci Eng C Mater Biol Appl*. Mar 1 2017;72:433-443. https://doi.org/10.1016/j.msec.2016.11.019
23. Boucq P, Ucakar B, Debuisson F, et al. High Internal Phase Emulsion-Templated Hydrophilic Polyphosphoester Scaffolds: Tailoring the Porosity and Degradation for Soft Tissue Engineering. *Biomacromolecules*. Mar 10 2025;26(3):1935-1947. https://doi.org/10.1021/acs.biomac.4c01740
24. Gangolphe L, Leon-Valdivieso CY, Nottelet B, et al. Electrospun microstructured PLA-based scaffolds featuring relevant anisotropic, mechanical and degradation characteristics for soft tissue engineering. *Mater Sci Eng C Mater Biol Appl*. Oct 2021;129:112339. https://doi.org/10.1016/j.msec.2021.112339
25. Patel S, Ziai K, Lighthall JG, Walen SG. Biologics and acellular dermal matrices in head and neck reconstruction: A comprehensive review. *Am J Otolaryngol*. Jan-Feb 2022;43(1):103233. https://doi.org/10.1016/j.amjoto.2021.103233
26. Walter RJ, Matsuda T, Reyes HM, Walter JM, Hanumadass M. Characterization of acellular dermal matrices (ADMs) prepared by two different methods. *Burns*. Mar 1998;24(2):104-13. https://doi.org/10.1016/s0305-4179(97)00110-1
27. Hoganson DM, O'Doherty EM, Owens GE, et al. The retention of extracellular matrix proteins and angiogenic and mitogenic cytokines in a decellularized porcine dermis. *Biomaterials*. Sep 2010;31(26):6730-7. https://doi.org/10.1016/j.biomaterials.2010.05.019
28. Wang H, Sun WQ. Comparative proteomic analysis of regenerative acellular matrices: The effects of tissue source and processing method. *J Biomed Mater Res B Appl Biomater*. Dec 2023;111(12):2002-2012. https://doi.org/10.1002/jbm.b.35300
29. Bondioli E, Fini M, Veronesi F, et al. Development and evaluation of a decellularized membrane from human dermis. *J Tissue Eng Regen Med*. Apr 2014;8(4):325-36. https://doi.org/10.1002/term.1530
30. Negenborn VL, Young-Afat DA, Dikmans REG, et al. Quality of life and patient satisfaction after one-stage implant-based breast reconstruction with an acellular dermal matrix versus two-stage breast reconstruction

 doi:10.20944/preprints202603.1941.v1

(BRIOS): primary outcome of a randomised, controlled trial. *Lancet Oncol*. Sep 2018;19(9):1205-1214. https://doi.org/10.1016/S1470-2045(18)30378-4

31. Spear SL, Sher SR, Al-Attar A. Focus on technique: supporting the soft-tissue envelope in breast reconstruction. *Plast Reconstr Surg*. Nov 2012;130(5 Suppl 2):89S-94S. https://doi.org/10.1097/PRS.0b013e3182625852
32. Salzberg CA, Ashikari AY, Berry C, Hunsicker LM. Acellular Dermal Matrix-Assisted Direct-to-Implant Breast Reconstruction and Capsular Contracture: A 13-Year Experience. *Plast Reconstr Surg*. Aug 2016;138(2):329-337. https://doi.org/10.1097/PRS.0000000000002331
33. Nolan IT, Farajzadeh MM, Boyd CJ, Bekisz JM, Gibson EG, Salibian AA. Do we need acellular dermal matrix in prepectoral breast reconstruction? A systematic review and meta-analysis. *J Plast Reconstr Aesthet Surg*. Nov 2023;86:251-260. https://doi.org/10.1016/j.bjps.2023.09.042
34. Janis JE, O'Neill AC, Ahmad J, Zhong T, Hofer SOP. Acellular dermal matrices in abdominal wall reconstruction: a systematic review of the current evidence. *Plast Reconstr Surg*. Nov 2012;130(5 Suppl 2):183S-193S. https://doi.org/10.1097/PRS.0b013e3182605cfc
35. Iorio ML, Shuck J, Attinger CE. Wound healing in the upper and lower extremities: a systematic review on the use of acellular dermal matrices. *Plast Reconstr Surg*. Nov 2012;130(5 Suppl 2):232S-241S. https://doi.org/10.1097/PRS.0b013e3182615703
36. Said HK, Bevers M, Butler CE. Reconstruction of the pelvic floor and perineum with human acellular dermal matrix and thigh flaps following pelvic exenteration. *Gynecol Oncol*. Dec 2007;107(3):578-82. https://doi.org/10.1016/j.ygyno.2007.08.063
37. Romano V, Belviso I, Cozzolino D, et al. Decellularization for the Preparation of Highly Preserved Human Acellular Skin Matrix for Regenerative Medicine. *J Vis Exp*. Sep 8 2021;(175)doi:10.3791/62935
38. Mansour RN, Karimizade A, Enderami SE, et al. The effect of source animal age, decellularization protocol, and sterilization method on bovine acellular dermal matrix as a scaffold for wound healing and skin regeneration. *Artif Organs*. Feb 2023;47(2):302-316. https://doi.org/10.1111/aor.14415
39. Stefanelli V, Lombardi J, Ferrer J, Gardocki-Sandor M. Vascularization of Human Acellular Dermal Matrices: A Comparative Study in a Nonhuman Primate Model. *Tissue Eng Part A*. May 2025;31(9-10):419-432. https://doi.org/10.1089/ten.TEA.2024.0059
40. Lindsey JT, Boyd CJ, Davis CB, Wilson JT, Kurapati S, de la Torre JI. Alloderm and Cortiva Have Similar Perioperative Wound Complications in Abdominal Wall Reconstruction. *J Surg Res*. Nov 2020;255:255-260. https://doi.org/10.1016/j.jss.2020.05.060
41. Gaster RS, Berger AJ, Monica SD, Sweeney RT, Endress R, Lee GK. Histologic analysis of fetal bovine derived acellular dermal matrix in tissue expander breast reconstruction. *Ann Plast Surg*. Apr 2013;70(4):447-53. https://doi.org/10.1097/SAP.0b013e31827e55af
42. Rodriguez JJ, Kung T, Wang Y, et al. Changes in Skin Vascularity in a Murine Model for Postmastectomy Radiation. *Ann Plast Surg*. May 2016;76(5):494-8. https://doi.org/10.1097/SAP.0000000000000628
43. Verginadis, II, Citrin DE, Ky B, et al. Radiotherapy toxicities: mechanisms, management, and future directions. *Lancet*. Jan 25 2025;405(10475):338-352. https://doi.org/10.1016/S0140-6736(24)02319-5
44. Bian X, Piipponen M, Liu Z, et al. Epigenetic memory of radiotherapy in dermal fibroblasts impairs wound repair capacity in cancer survivors. *Nat Commun*. Oct 28 2024;15(1):9286. https://doi.org/10.1038/s41467-024-53295-1
45. Parmeshwar N, Knox JA, Piper ML. Evaluation of Pre-Pectoral Direct-to-Implant Breast Reconstruction with Post-Mastectomy Radiation: A Systematic Review and Meta-Analysis. *J Clin Med*. Jul 15 2025;14(14)doi:10.3390/jcm14145004
46. Myckatyn TM, Cavallo JA, Sharma K, et al. The impact of chemotherapy and radiation therapy on the remodeling of acellular dermal matrices in staged, prosthetic breast reconstruction. *Plast Reconstr Surg*. Jan 2015;135(1):43e-57e. https://doi.org/10.1097/PRS.0000000000000807
47. Ohlinger R, Nawroth F, Kohlmann T, et al. Retrospective Study of Radiotherapy Impact on the Outcome of Material-assisted Implant-based Subpectoral Breast Reconstruction. *Anticancer Res*. Apr 2021;41(4):2017-2024. https://doi.org/10.21873/anticanres.14969

 doi:10.20944/preprints202603.1941.v1

48. Lisa A, Carbonaro R, Bottoni M, Ostapenko E, Rietjens M. Bovine Acellular Dermal Matrix-Based Breast Reconstruction in Previously Irradiated Breasts: Complications and Outcomes From a Single-Center Experience. *Ann Plast Surg*. Dec 1 2023;91(6):686-692. https://doi.org/10.1097/SAP.0000000000003667
49. Faulkner HR, Shikowitz-Behr L, McLeod M, Wright E, Hulsen J, Austen WG, Jr. The Use of Absorbable Mesh in Implant-Based Breast Reconstruction: A 7-Year Review. *Plast Reconstr Surg*. Dec 2020;146(6):731e-736e. https://doi.org/10.1097/PRS.0000000000007384
50. Arnautovic A, Williams S, Ash M, Menon A, Shauly O, Losken A. Outcomes in Implant-Based Breast Reconstruction Utilizing Biosynthetic Mesh: A Meta-Analysis. *Aesthet Surg J*. Jan 7 2025;doi:10.1093/asj/sjaf002
51. Janzekovic J, Hunt J, Peltz T, Wagels M, Brown T, Hutmacher DW. Biomechanical Principles of Breast Implants and Current State of Research in Soft Tissue Engineering for Cosmetic Breast Augmentation. *Aesthetic Plast Surg*. Feb 2022;46(1):1-10. https://doi.org/10.1007/s00266-021-02559-y
52. Karp N, Sorenson TJ, Boyd CJ, et al. The GalaFLEX "Empanada" for Direct-to-Implant Prepectoral Breast Reconstruction. *Plast Reconstr Surg*. Mar 01 2025;155(3):488e-491e. https://doi.org/10.1097/PRS.0000000000011592
53. Sorenson TJ, Boyd CJ, Hemal K, et al. Outcome of Prepectoral Direct-to-Implant Breast Reconstruction With the Poly-4-hydroxybutyrate Wrap. *Plast Reconstr Surg Glob Open*. Nov 2025;13(11):e7268. https://doi.org/10.1097/GOX.0000000000007268
54. Vernice NA, Boyd CJ, Hemal K, et al. Systematic Review of Poly-4-Hydroxybutyrate in Modern Breast Surgery. *Aesthet Surg J*. Jun 21 2025;doi:10.1093/asj/sjaf099
55. Vegas MR, Martin del Yerro JL. Stiffness, compliance, resilience, and creep deformation: understanding implant-soft tissue dynamics in the augmented breast: fundamentals based on materials science. *Aesthetic Plast Surg*. Oct 2013;37(5):922-30. https://doi.org/10.1007/s00266-013-0197-y
56. Potter S, Conroy EJ, Cutress RI, et al. Short-term safety outcomes of mastectomy and immediate implant-based breast reconstruction with and without mesh (iBRA): a multicentre, prospective cohort study. *Lancet Oncol*. Feb 2019;20(2):254-266. https://doi.org/10.1016/S1470-2045(18)30781-2
57. Frey JD, Salibian AA, Choi M, Karp NS. The Importance of Tissue Perfusion in Reconstructive Breast Surgery. *Plast Reconstr Surg*. Jul 2019;144(1S Utilizing a Spectrum of Cohesive Implants in Aesthetic and Reconstructive Breast Surgery):21S-29S. https://doi.org/10.1097/PRS.0000000000005947
58. Sadtler K, Wolf MT, Ganguly S, et al. Divergent immune responses to synthetic and biological scaffolds. *Biomaterials*. Feb 2019;192:405-415. https://doi.org/10.1016/j.biomaterials.2018.11.002
59. Bae JY, Shim J, Hwang S, et al. Evaluating the Biocompatibility and Efficacy of Absorbable Three-Dimensional Micro-Nanofiber Scaffolds for Volume Restoration Following Post-Mastectomy Breast Reconstruction: An Experimental Study. *J Clin Med*. May 27 2025;14(11)doi:10.3390/jcm14113754
60. Van Natta BW, Pineda Molina C, Antonelli V, Hussey GS, Badylak SF. Histomorphologic Outcomes of GalaFLEX Scaffold Used in Breast Surgery: Clinical Follow-up From 6 Weeks to 63 Months. *Aesthet Surg J*. Oct 16 2025;45(11):1130-1140. https://doi.org/10.1093/asj/sjaf100
61. Campillo-Fernandez AJ, Unger RE, Peters K, et al. Analysis of the biological response of endothelial and fibroblast cells cultured on synthetic scaffolds with various hydrophilic/hydrophobic ratios: influence of fibronectin adsorption and conformation. *Tissue Eng Part A*. Jun 2009;15(6):1331-41. https://doi.org/10.1089/ten.tea.2008.0146
62. Ma S, Feng X, Liu F, Wang B, Zhang H, Niu X. The pro-inflammatory response of macrophages regulated by acid degradation products of poly(lactide-co-glycolide) nanoparticles. *Eng Life Sci*. Oct 2021;21(10):709-720. https://doi.org/10.1002/elsc.202100040
63. Sung HJ, Meredith C, Johnson C, Galis ZS. The effect of scaffold degradation rate on three-dimensional cell growth and angiogenesis. *Biomaterials*. Nov 2004;25(26):5735-42. https://doi.org/10.1016/j.biomaterials.2004.01.066
64. Chian KS, Leong MF, Kono K. Regenerative medicine for oesophageal reconstruction after cancer treatment. *Lancet Oncol*. Feb 2015;16(2):e84-92. https://doi.org/10.1016/S1470-2045(14)70410-3
65. Janouskova O. Synthetic polymer scaffolds for soft tissue engineering. *Physiol Res*. Oct 30 2018;67(Suppl 2):S335-S348. https://doi.org/10.33549/physiolres.933983

 doi:10.20944/preprints202603.1941.v1

66. Panayi AC, Orgill DP. Current Use of Biological Scaffolds in Plastic Surgery. *Plast Reconstr Surg*. Jan 2019;143(1):209-220. https://doi.org/10.1097/PRS.0000000000005102
67. Becker H, Lind Ii JG. The Use of Synthetic Mesh in Reconstructive, Revision, and Cosmetic Breast Surgery. *Aesthetic Plast Surg*. Aug 2020;44(4):1120-1127. https://doi.org/10.1007/s00266-020-01822-y
68. Levy AS, Bernstein JL, Xia JJ, Otterburn DM. Poly-4-Hydroxybutyric Acid Mesh Compares Favorably With Acellular Dermal Matrix in Tissue Expander-Based Breast Reconstruction. *Ann Plast Surg*. Jul 2020;85(S1 Suppl 1):S2-S7. https://doi.org/10.1097/SAP.0000000000002339
69. Zhu LM, Schuster P, Klinge U. Mesh implants: An overview of crucial mesh parameters. *World J Gastrointest Surg*. Oct 27 2015;7(10):226-36. https://doi.org/10.4240/wjgs.v7.i10.226
70. Zhang F, King MW. Biodegradable Polymers as the Pivotal Player in the Design of Tissue Engineering Scaffolds. *Adv Healthc Mater*. Jul 2020;9(13):e1901358. https://doi.org/10.1002/adhm.201901358
71. Jiang B, Akar B, Waller TM, Larson JC, Appel AA, Brey EM. Design of a composite biomaterial system for tissue engineering applications. *Acta Biomater*. Mar 2014;10(3):1177-86. https://doi.org/10.1016/j.actbio.2013.11.029
72. Setayeshmehr M, Esfandiari E, Rafieinia M, et al. Hybrid and Composite Scaffolds Based on Extracellular Matrices for Cartilage Tissue Engineering. *Tissue Eng Part B Rev*. Jun 2019;25(3):202-224. https://doi.org/10.1089/ten.TEB.2018.0245
73. Sadr N, Pippenger BE, Scherberich A, et al. Enhancing the biological performance of synthetic polymeric materials by decoration with engineered, decellularized extracellular matrix. *Biomaterials*. Jul 2012;33(20):5085-93. https://doi.org/10.1016/j.biomaterials.2012.03.082
74. Goyal R, Vega ME, Pastino AK, et al. Development of hybrid scaffolds with natural extracellular matrix deposited within synthetic polymeric fibers. *J Biomed Mater Res A*. Aug 2017;105(8):2162-2170. https://doi.org/10.1002/jbm.a.36078
75. Sawadkar P, Mohanakrishnan J, Rajasekar P, et al. A Synergistic Relationship between Polycaprolactone and Natural Polymers Enhances the Physical Properties and Biological Activity of Scaffolds. *ACS Appl Mater Interfaces*. Mar 25 2020;12(12):13587-13597. https://doi.org/10.1021/acsami.9b19715
76. Donnely E, Griffin M, Butler PE. Breast Reconstruction with a Tissue Engineering and Regenerative Medicine Approach (Systematic Review). *Ann Biomed Eng*. Jan 2020;48(1):9-25. https://doi.org/10.1007/s10439-019-02373-3
77. Bonito V, Smits A, Goor O, et al. Modulation of macrophage phenotype and protein secretion via heparin-IL-4 functionalized supramolecular elastomers. *Acta Biomater*. Apr 15 2018;71:247-260. https://doi.org/10.1016/j.actbio.2018.02.032
78. Song Y, Li L, Zhao W, et al. Surface modification of electrospun fibers with mechano-growth factor for mitigating the foreign-body reaction. *Bioact Mater*. Sep 2021;6(9):2983-2998. https://doi.org/10.1016/j.bioactmat.2021.02.020
79. Kao WJ, Lee D. In vivo modulation of host response and macrophage behavior by polymer networks grafted with fibronectin-derived biomimetic oligopeptides: the role of RGD and PHSRN domains. *Biomaterials*. Nov 2001;22(21):2901-9. https://doi.org/10.1016/s0142-9612(01)00037-0
80. Klimek K, Ginalska G. Proteins and Peptides as Important Modifiers of the Polymer Scaffolds for Tissue Engineering Applications-A Review. *Polymers (Basel)*. Apr 6 2020;12(4)doi:10.3390/polym12040844
81. Mukasheva F, Adilova L, Dyussenbinov A, Yernaimanova B, Abilev M, Akilbekova D. Optimizing scaffold pore size for tissue engineering: insights across various tissue types. *Front Bioeng Biotechnol*. 2024;12:1444986. https://doi.org/10.3389/fbioe.2024.1444986
82. Mehdizadeh H, Sumo S, Bayrak ES, Brey EM, Cinar A. Three-dimensional modeling of angiogenesis in porous biomaterial scaffolds. *Biomaterials*. Apr 2013;34(12):2875-87. https://doi.org/10.1016/j.biomaterials.2012.12.047
83. Pedram P, Mazio C, Imparato G, Netti PA, Salerno A. Spatial patterning of PCLmicro-scaffolds directs 3D vascularized bio-constructs morphogenesisin vitro. *Biofabrication*. Aug 18 2022;14(4)doi:10.1088/1758-5090/ac8620

 doi:10.20944/preprints202603.1941.v1

84. Anderson AR, Caston ELP, Riley L, et al. Engineering the microstructure and spatial bioactivity of MAP scaffolds instructs vasculogenesis in vitro and modifies vessel formation in vivo. *Adv Funct Mater*. Jan 15 2025;35(3)doi:10.1002/adfm.202400567
85. Li D, Hou L, Meng Z, Zhang J. Enhancing soft tissue regeneration with a 3D-printed Exos@GelMA+PCL biohybrid scaffold via M2 macrophage polarization. *Biomed Mater*. Nov 19 2025;20(6)doi:10.1088/1748-605X/ae1d02
86. Xu M, Su T, Jin X, et al. Inflammation-mediated matrix remodeling of extracellular matrix-mimicking biomaterials in tissue engineering and regenerative medicine. *Acta Biomater*. Oct 1 2022;151:106-117. https://doi.org/10.1016/j.actbio.2022.08.015
87. Venugopal D, Vishwakarma S, Kaur I, Samavedi S. Electrospun fiber-based strategies for controlling early innate immune cell responses: Towards immunomodulatory mesh designs that facilitate robust tissue repair. *Acta Biomater*. Jun 2023;163:228-247. https://doi.org/10.1016/j.actbio.2022.06.004
88. Larsen A, Rasmussen LE, Rasmussen LF, et al. Histological Analyses of Capsular Contracture and Associated Risk Factors: A Systematic Review. *Aesthetic Plast Surg*. Dec 2021;45(6):2714-2728. https://doi.org/10.1007/s00266-021-02473-3
89. Kiseleva V, Bagdasarian A, Vishnyakova P, et al. Three-Dimensional Disassemblable Scaffolds for Breast Reconstruction. *Polymers (Basel)*. Jul 25 2025;17(15)doi:10.3390/polym17152036
90. Teixeira AM, Martins P. A review of bioengineering techniques applied to breast tissue: Mechanical properties, tissue engineering and finite element analysis. *Front Bioeng Biotechnol*. 2023;11:1161815. https://doi.org/10.3389/fbioe.2023.1161815
91. Sultana N, Cole A, Strachan F. Biocomposite Scaffolds for Tissue Engineering: Materials, Fabrication Techniques and Future Directions. *Materials (Basel)*. Nov 15 2024;17(22)doi:10.3390/ma17225577
92. Abdul-Al M, Zaernia A, Sefat F. Biomaterials for breast reconstruction: Promises, advances, and challenges. *J Tissue Eng Regen Med*. Nov 2020;14(11):1549-1569. https://doi.org/10.1002/term.3121
93. Masson-Meyers DS, Tayebi L. Vascularization strategies in tissue engineering approaches for soft tissue repair. *J Tissue Eng Regen Med*. Sep 2021;15(9):747-762. https://doi.org/10.1002/term.3225
94. Joshi A, Choudhury S, Gugulothu SB, Visweswariah SS, Chatterjee K. Strategies to Promote Vascularization in 3D Printed Tissue Scaffolds: Trends and Challenges. *Biomacromolecules*. Jul 11 2022;23(7):2730-2751. https://doi.org/10.1021/acs.biomac.2c00423
95. Sorenson TJ, Romanowski L, Boyd CJ, et al. Outcomes after Wise-Pattern Mastectomy with the Inferior Dermal Flap in the Prepectoral Setting: A Systematic Review and Meta-Analysis. *Plast Reconstr Surg*. Mar 18 2026;doi:10.1097/PRS.0000000000013040
96. Bland E, Dreau D, Burg KJ. Overcoming hypoxia to improve tissue-engineering approaches to regenerative medicine. *J Tissue Eng Regen Med*. Jul 2013;7(7):505-14. https://doi.org/10.1002/term.540
97. Fiedler T, Belova IV, Murch GE, et al. A comparative study of oxygen diffusion in tissue engineering scaffolds. *J Mater Sci Mater Med*. Nov 2014;25(11):2573-8. https://doi.org/10.1007/s10856-014-5264-7
98. Ehsan SM, George SC. Nonsteady state oxygen transport in engineered tissue: implications for design. *Tissue Eng Part A*. Jun 2013;19(11-12):1433-42. https://doi.org/10.1089/ten.TEA.2012.0587
99. Serbo JV, Gerecht S. Vascular tissue engineering: biodegradable scaffold platforms to promote angiogenesis. *Stem Cell Res Ther*. Jan 24 2013;4(1):8. https://doi.org/10.1186/scrt156
100. Nillesen ST, Geutjes PJ, Wismans R, Schalkwijk J, Daamen WF, van Kuppevelt TH. Increased angiogenesis and blood vessel maturation in acellular collagen-heparin scaffolds containing both FGF2 and VEGF. *Biomaterials*. Feb 2007;28(6):1123-31. https://doi.org/10.1016/j.biomaterials.2006.10.029
101. Davies NH, Schmidt C, Bezuidenhout D, Zilla P. Sustaining neovascularization of a scaffold through staged release of vascular endothelial growth factor-A and platelet-derived growth factor-BB. *Tissue Eng Part A*. Jan 2012;18(1-2):26-34. https://doi.org/10.1089/ten.tea.2011.0192
102. Xia P, Luo Y. Vascularization in tissue engineering: The architecture cues of pores in scaffolds. *J Biomed Mater Res B Appl Biomater*. May 2022;110(5):1206-1214. https://doi.org/10.1002/jbm.b.34979
103. Xiao X, Wang W, Liu D, et al. The promotion of angiogenesis induced by three-dimensional porous beta-tricalcium phosphate scaffold with different interconnection sizes via activation of PI3K/Akt pathways. *Sci Rep*. Mar 23 2015;5:9409. https://doi.org/10.1038/srep09409

 doi:10.20944/preprints202603.1941.v1

104. Wang WY, Kent RN, 3rd, Huang SA, et al. Direct comparison of angiogenesis in natural and synthetic biomaterials reveals that matrix porosity regulates endothelial cell invasion speed and sprout diameter. *Acta Biomater*. Nov 2021;135:260-273. https://doi.org/10.1016/j.actbio.2021.08.038
105. Ekaputra AK, Prestwich GD, Cool SM, Hutmacher DW. The three-dimensional vascularization of growth factor-releasing hybrid scaffold of poly (epsilon-caprolactone)/collagen fibers and hyaluronic acid hydrogel. *Biomaterials*. Nov 2011;32(32):8108-17. https://doi.org/10.1016/j.biomaterials.2011.07.022
106. Martin JR, Gupta MK, Page JM, et al. A porous tissue engineering scaffold selectively degraded by cell-generated reactive oxygen species. *Biomaterials*. Apr 2014;35(12):3766-76. https://doi.org/10.1016/j.biomaterials.2014.01.026
107. Salerno A, Palladino A, Pizzoleo C, Attanasio C, Netti PA. Computer-aided patterning of PCL microspheres to build modular scaffolds featuring improved strength and neovascularized tissue integration. *Biofabrication*. Jul 6 2022;14(4)doi:10.1088/1758-5090/ac7ad8
108. Pattnaik A, Sanket AS, Pradhan S, et al. Designing of gradient scaffolds and their applications in tissue regeneration. *Biomaterials*. May 2023;296:122078. https://doi.org/10.1016/j.biomaterials.2023.122078
109. Golas AR, Hernandez KA, Spector JA. Tissue engineering for plastic surgeons: a primer. *Aesthetic Plast Surg*. Feb 2014;38(1):207-221. https://doi.org/10.1007/s00266-013-0255-5
110. Kronowitz SJ, Robb GL. Radiation therapy and breast reconstruction: a critical review of the literature. *Plast Reconstr Surg*. Aug 2009;124(2):395-408. https://doi.org/10.1097/PRS.0b013e3181aee987
111. Cavallo JA, Gangopadhyay N, Dudas J, et al. Remodeling Characteristics and Collagen Distributions of Biologic Scaffold Materials Biopsied From Postmastectomy Breast Reconstruction Sites. *Ann Plast Surg*. Jul 2015;75(1):74-83. https://doi.org/10.1097/SAP.0000000000000538
112. Badylak SF. Decellularized allogeneic and xenogeneic tissue as a bioscaffold for regenerative medicine: factors that influence the host response. *Ann Biomed Eng*. Jul 2014;42(7):1517-27. https://doi.org/10.1007/s10439-013-0963-7
113. Makarewicz N, Perrault D, Sharma A, et al. Comparing the Outcomes and Complication Rates of Biologic vs Synthetic Meshes in Implant-Based Breast Reconstruction: A Systematic Review. *Ann Plast Surg*. May 1 2023;90(5):516-527. https://doi.org/10.1097/SAP.0000000000003512
114. Zhang J, An R, Yu ZH, Zhang L. Comparison of outcomes following prepectoral and subpectoral implants for breast reconstruction in patients with breast cancer. *Front Oncol*. 2024;14:1499710. https://doi.org/10.3389/fonc.2024.1499710
115. Chen Y, Wang ML, Black GG, Bernstein JL, Chinta M, Otterburn DM. Timeline and Incidence of Postoperative Complications in Prepectoral, Dual-Plane, and Total Submuscular Alloplastic Reconstruction With and Without Biosynthetic Scaffold Usage. *Ann Plast Surg*. Jun 1 2023;90(6S Suppl 5):S466-S471. https://doi.org/10.1097/SAP.0000000000003482
116. Park JU, Ham J, Kim S, et al. Alleviation of capsular formations on silicone implants in rats using biomembrane-mimicking coatings. *Acta Biomater*. Oct 2014;10(10):4217-25. https://doi.org/10.1016/j.actbio.2014.07.007
117. Karinja SJ, Bernstein JL, Mukherjee S, et al. An Antifibrotic Breast Implant Surface Coating Significantly Reduces Periprosthetic Capsule Formation. *Plast Reconstr Surg*. Oct 1 2023;152(4):775-785. https://doi.org/10.1097/PRS.0000000000010323
118. Paul M, Lee W, Song WJ, Im J. Electrospun polycaprolactone fibers encapsulating omega-3 and montelukast sodium to prevent capsular contracture in breast implant surgery. *Int J Pharm*. Jun 30 2025;679:125744. https://doi.org/10.1016/j.ijpharm.2025.125744
119. Cottler PS, Olenczak JB, Ning B, et al. Fenestration Improves Acellular Dermal Matrix Biointegration: An Investigation of Revascularization with Photoacoustic Microscopy. *Plast Reconstr Surg*. Apr 2019;143(4):971-981. https://doi.org/10.1097/PRS.0000000000005410
120. Lisk R, Hemal K, Boyd CJ, Karp NS, Choi M, Cohen O. Soft Tissue Support Use in Implant-Based Breast Reconstruction: A Nationwide, Cross-Sectional Study of Postoperative Complications. *Ann Plast Surg*. Feb 17 2026;doi:10.1097/SAP.0000000000004660
121. Zhang X, Du Z, Wang Z, Luo C, Sun J. Current progress of bio-fabrication in breast reconstruction. *Acta Biomater*. Mar 2026;212:145-167. https://doi.org/10.1016/j.actbio.2026.01.015

 doi:10.20944/preprints202603.1941.v1

122. Webber MJ, Khan OF, Sydlik SA, Tang BC, Langer R. A perspective on the clinical translation of scaffolds for tissue engineering. *Ann Biomed Eng*. Mar 2015;43(3):641-56. https://doi.org/10.1007/s10439-014-1104-7
123. Whitaker R, Hernaez-Estrada B, Hernandez RM, Santos-Vizcaino E, Spiller KL. Immunomodulatory Biomaterials for Tissue Repair. *Chem Rev*. Sep 22 2021;121(18):11305-11335. https://doi.org/10.1021/acs.chemrev.0c00895
124. Yao T, Wieringa PA, Chen H, et al. Fabrication of a self-assembled honeycomb nanofibrous scaffold to guide endothelial morphogenesis. *Biofabrication*. Jul 16 2020;12(4):045001. https://doi.org/10.1088/1758-5090/ab9988
125. Zhang W, Wray LS, Rnjak-Kovacina J, et al. Vascularization of hollow channel-modified porous silk scaffolds with endothelial cells for tissue regeneration. *Biomaterials*. Jul 2015;56:68-77. https://doi.org/10.1016/j.biomaterials.2015.03.053
126. Li S, Liu YY, Liu LJ, Hu QX. A Versatile Method for Fabricating Tissue Engineering Scaffolds with a Three-Dimensional Channel for Prevasculature Networks. *ACS Appl Mater Interfaces*. Sep 28 2016;8(38):25096-103. https://doi.org/10.1021/acsami.6b07725
127. He YJ, Santana MF, Staneviciute A, et al. Cell-Laden Gradient Hydrogel Scaffolds for Neovascularization of Engineered Tissues. *Adv Healthc Mater*. Apr 2021;10(7):e2001706. https://doi.org/10.1002/adhm.202001706
128. Wang Y, Chen S, Liang H, Bai J. A review of graded scaffolds made by additive manufacturing for tissue engineering: design, fabrication and properties. *Biofabrication*. Mar 12 2025;17(2)doi:10.1088/1758-5090/adba8e
129. Sinha R, Camara-Torres M, Scopece P, et al. A hybrid additive manufacturing platform to create bulk and surface composition gradients on scaffolds for tissue regeneration. *Nat Commun*. Jan 21 2021;12(1):500. https://doi.org/10.1038/s41467-020-20865-y
130. Wong HK, Ivan Lam CR, Wen F, et al. Novel method to improve vascularization of tissue engineered constructs with biodegradable fibers. *Biofabrication*. Jan 7 2016;8(1):015004. https://doi.org/10.1088/1758-5090/8/1/015004
131. Rnjak-Kovacina J, Gerrand YW, Wray LS, et al. Vascular Pedicle and Microchannels: Simple Methods Toward Effective In Vivo Vascularization of 3D Scaffolds. *Adv Healthc Mater*. Dec 2019;8(24):e1901106. https://doi.org/10.1002/adhm.201901106
132. An X, Chong PL, Zohourkari I, et al. Mechanical influence of tissue scaffolding design with different geometries using finite element study. *Proc Inst Mech Eng H*. Aug 2023;237(8):1008-1016. https://doi.org/10.1177/09544119231187685
133. Biglari N, Razzaghi M, Afkham Y, Azimi G, Gross JD, Samadi A. Advanced biomaterials in immune modulation: The future of regenerative therapies. *Int J Pharm*. Sep 15 2025;682:125972. https://doi.org/10.1016/j.ijpharm.2025.125972
134. Salthouse D, Novakovic K, Hilkens CMU, Ferreira AM. Interplay between biomaterials and the immune system: Challenges and opportunities in regenerative medicine. *Acta Biomater*. Jan 1 2023;155:1-18. https://doi.org/10.1016/j.actbio.2022.11.003
135. Berger LE, Spoer DL, Huffman SS, et al. Acellular Dermal Matrix-Assisted, Prosthesis-Based Breast Reconstruction: A Comparison of SurgiMend PRS, AlloDerm, and DermACELL. *Ann Plast Surg*. Jul 1 2024;93(1):34-42. https://doi.org/10.1097/SAP.0000000000003990
136. Hong Z, Chen D. A commentary on "Recurrence of breast cancer after reconstruction with macro-textured silicone breast implants: a retrospective cohort study". *Int J Surg*. Oct 1 2025;111(10):7445-7446. https://doi.org/10.1097/JS9.0000000000002832
137. Wu Y, Ding X, Wang Y, Ouyang D. Harnessing the power of machine learning into tissue engineering: current progress and future prospects. *Burns Trauma*. 2024;12:tkae053. https://doi.org/10.1093/burnst/tkae053
138. Puls TJ, Fisher CS, Cox A, et al. Regenerative tissue filler for breast conserving surgery and other soft tissue restoration and reconstruction needs. *Sci Rep*. Feb 1 2021;11(1):2711. https://doi.org/10.1038/s41598-021-81771-x
139. Bertsch P, Diba M, Mooney DJ, Leeuwenburgh SCG. Self-Healing Injectable Hydrogels for Tissue Regeneration. *Chem Rev*. Jan 25 2023;123(2):834-873. https://doi.org/10.1021/acs.chemrev.2c00179

 doi:10.20944/preprints202603.1941.v1

140. Mollaheydaralimoazzen M, Sheikholeslam M, Poursamar SA, Farzan M, Farzan M, Rafienia M. 3D-printing of shear-thinning and self-healing gelatin/starch/halloysite-nanotube hydrogels for soft tissue engineering: An in vitro and in vivo assessment. *Int J Biol Macromol*. Jun 2025;315(Pt 2):144502. https://doi.org/10.1016/j.ijbiomac.2025.144502
141. Goder Orbach D, Roitman I, Coster Kimhi G, Zilberman M. Formulation-Property Effects in Novel Injectable and Resilient Natural Polymer-Based Hydrogels for Soft Tissue Regeneration. *Polymers (Basel)*. Oct 12 2024;16(20)doi:10.3390/polym16202879
142. Liao J, Timoshenko AB, Cordova DJ, et al. Propelling Minimally Invasive Tissue Regeneration With Next-Era Injectable Pre-Formed Scaffolds. *Adv Mater*. Aug 2024;36(33):e2400700. https://doi.org/10.1002/adma.202400700