Tissue engineering strategies for breast reconstruction: a literature review of current advances and future directions

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Background and Objective: Mastectomy is a primary treatment for breast cancer patients, and both autologous and implant-based reconstructive techniques have shown excellent results. In recent years, advancements in bioengineering have led to a proliferation of innovative approaches to breast reconstruction. This article comprehensively explores the promising perspectives offered by bioengineering and tissue engineering in the field of breast reconstruction.

Methods: A literature review was conducted between April and June 2023 on PubMed and Google Scholar Databases. All English and French articles related to bioengineering applied to the field of breast reconstruction were included. We used the Evidence-Based Veterinary Medicine Association (EBVM) Toolkit 14 checklist for narrative reviews as a quality assurance measure and the Scale for the Assessment of Narrative Review Articles (SANRA) tool to self-assess our methodology.

Key Content and Findings: Over 130 references related to breast bioengineering were included. The analysis revealed four key applications: enhancing the quality of the skin envelope, improving the viability of fat grafting, creating breast shape and volume via bio-printing, and optimizing nipple reconstruction through engineering techniques. The primary identified approaches revolved around establishing structural support and enhancing cellular viability. Structural techniques predominantly involved the implementation of 3D printed, decellularized, or biocompatible material scaffolds. Meanwhile, promoting cellular content

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trophicity primarily focused on harnessing the regenerative potential of adipose-derived stem cells (ADSCs) and increasing the tissue's survivability and cell trophicity.

Conclusions: Tissue and bioengineering hold immense promise in the field of breast reconstruction, offering a diverse array of approaches. By combining existing techniques with novel advancements, they have the potential to significantly enhance the therapeutic options available to plastic and reconstructive surgeons.

Keywords: Breast surgery; breast reconstruction; tissue engineering; acellular matrix; scaffold

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Introduction

Background

Breast cancer is a significant health concern among women in the US, with over 280,000 new diagnoses in 2022 (1). Surgery is the most common treatment approach (2). Mastectomy, which involves removing the entire breast tissue, is a standard component of treatment for many patients with breast cancer. In contrast, nipple-sparing mastectomy (NSM) is a surgical technique that involves removing the breast tissue while sparing the nipple and areola complex (3). NSM is not considered a safe option for all breast cancer subtypes and cases, particularly those with multifocal tumors or hormone receptor-negative/ERBB2-positive subtypes (4,5). In such cases, total mastectomy remains the gold standard therapy. For both these approaches, reconstruction is an option proposed by the plastic surgeon and is chosen by up to 40% of the patients (2). Adjuvant radiotherapy and chemotherapy can obstruct reconstructive surgery by damaging the remaining soft tissues. Different techniques are clinically used to achieve total breast reconstruction while facing its challenges.

Implant-based techniques consist in reproducing the breast volume by using a silicon implant. In contrast, autologous techniques recreate the breast shape using various flaps (free or pedicled, fascio-cutaneous or musculocutaneous flaps) or exclusive fat grafting. Implant-based and autologous techniques can also be combined. Each of these techniques has advantages and downsides: Implant-based reconstruction following mastectomy is easy to perform, with moderate technicity (no fine dissection or microsurgery) and short operative time but is limited by the poor skin laxity and the long-term cosmetic outcomes due to capsule contracture (6). Moreover, multiple surgeries are needed due to the limited lifetime of current silicon implants (7). In contrast, autologous flaps provide a natural result that can be stable in time and avoid any foreign materials with all linked disadvantages (8). However, it requires a high degree of technical skills for the flap and pedicle dissection, longer surgeries, and may still need improvement despite recent microsurgery advances. Nipple-areolar complex (NAC) reconstruction has improved with the advent of 3D tattooing, but local flap techniques still need to provide a long-term projection of the nipple (9,10). Overall, all of these techniques still fail in recreating an identical breast and fully restoring the femininity of affected patients.

Rationale and knowledge gap

The importance of this article for the readership lies in its role in highlighting the evolution and potential of tissue engineering in the field of breast reconstruction. Tissue engineering, a concept introduced by Joseph Vacanti and Robert Langer in the late 1980s (11), offers a multidisciplinary approach that combines engineering, biology, and medicine to develop biological substitutes for damaged tissues and organs. While the initial applications of tissue engineering focused on cartilage regeneration (12,13), the rapid interest of breast surgeons in the unique properties of acellular dermal matrices (ADMs) and fat tissue processing opened up new avenues in breast reconstruction. Over the past two decades, numerous innovative concepts and applications of tissue and bioengineering have emerged in this field. By exploring these advancements, this article aims to provide valuable insights to readers, including researchers, clinicians, and medical professionals involved in breast reconstruction. It serves as a knowledge resource, showcasing the progress made in tissue engineering techniques and their potential impact on improving outcomes in breast reconstruction procedures.

Table 1 Search strategy summary

Items	Specification
Date of last search	June 6th, 2023
Databases and other sources searched	PubMed, Google Scholar
Search terms used	(I) Breast reconstruction AND Skin AND (Tissue Engineering OR Dermal Matri*)
	(II) Engineering AND (Fat graft* OR Lipo*) AND Breast reconstruction
	(III) Engineering AND Breast reconstruction AND (Printing OR Scaffold)
	(IV) Engineering AND Nipple reconstruction
Timeframe	Published after 2000
Inclusion and exclusion criteria	Inclusion criteria: articles reporting on tissue engineering or bioengineering-based techniques for breast reconstruction
	Exclusion criteria: language other than English or French
Selection process	Selection was independently conducted by the two first authors (Berkane Y and Oubari H), and consensus was obtained by the senior author (Lellouch AG) if needed

Objective

This work aims to review all the different applications of tissue and bioengineering in breast reconstruction and describe how surgeons can use it to improve the outcomes of these complex surgeries. We will explain the various techniques for each purpose: improving the skin envelope, increasing fat grafting trophicity, enhancing the breast shape and volume using 3D printing, and upgrading refinements through NAC reconstruction. We present this article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-23-1724/rc).

Methods

We performed a literature search on PubMed and Google Scholar Databases between April and June 2023. The search strategy (*Table 1*) excluded no species to include future directions. Articles published before 2000 and articles in languages other than English and French were excluded. To allow for a better focus on each sub-objective, we performed different searches for each purpose, using the following combination of keywords and Boolean operators:

(I) Breast reconstruction AND Skin AND (Tissue Engineering OR Dermal Matri*);
(II) Engineering AND (Fat graft* OR Lipo*) AND Breast reconstruction;
(III) Engineering AND Breast reconstruction AND (Printing OR Scaffold);
(IV) Engineering AND Nipple reconstruction.

This article used the Evidence-Based Veterinary Medicine Association (EBVM) Toolkit 14 checklist for narrative reviews as a quality assurance measure. Additionally, we used the Scale for the Assessment of Narrative Review Articles (SANRA) tool [2019] to self-assess our methodology (14). It is noted that these guidelines were not used to assess the quality of the included articles but rather to ensure the robustness and credibility of our research process.

Literature review of tissue- and bio-engineering approaches in breast reconstruction

Breast reconstruction aims to restore volume, texture, shape, and symmetry. Plastic surgeons use various techniques to achieve this, and engineering-based approaches have allowed significant advances (*Figure 1*).

Improving the quality (thickness and elasticity) of the skin envelope

ADMs have been extensively used in breast reconstruction for several decades. ADMs are skin matrices processed to remove all cells and antigenic elements, with a threshold of less than 50 ng/mg of tissue of double-stranded DNA (15). These matrices can be sourced from humans or animals (16-18) (*Figure 2*). They consist of collagen,

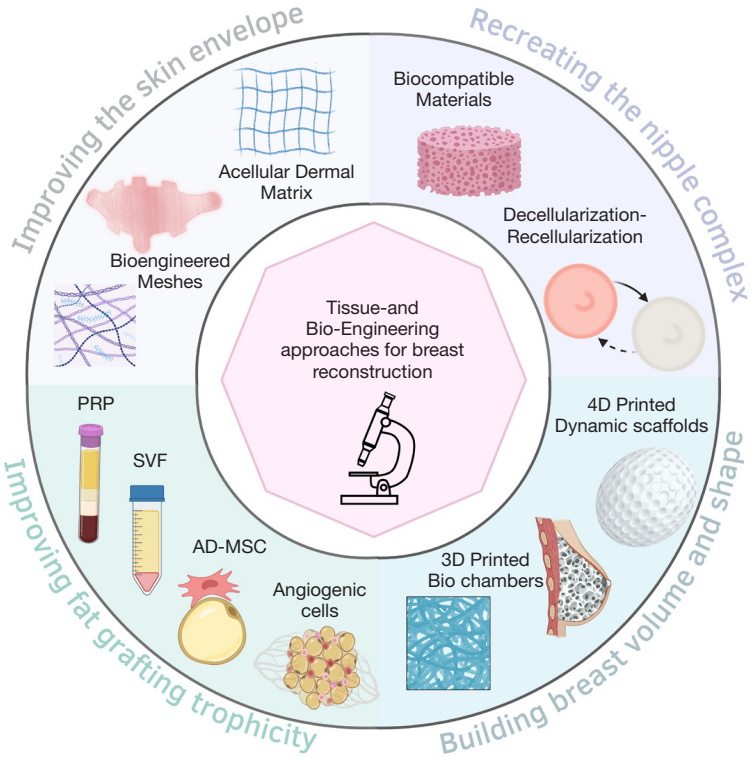

Figure 1 Tissue- and bio-engineering approaches applied to breast reconstruction. The objectives are to improve the skin envelope, shape, and volume retention through enhanced fat grafting and recipient scaffold and achieve long-term nipple-areolar complex reconstruction. AD-MSC, adipose-derived mesenchymal stem cells; PRP, platelet-rich plasma; SVF, stromal vascular fraction.

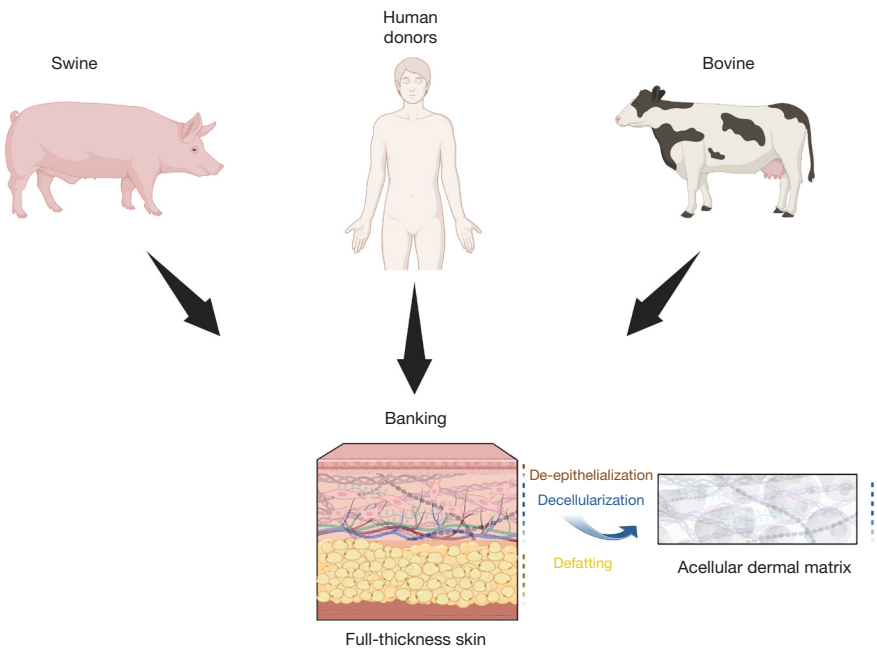

Figure 2 Acellular dermal matrices can be obtained from porcine, bovine, or human skin by de-epithelialization, defatting, and decellularization of the dermis.

elastic fibers, and other components of the extracellular matrix, such as fibronectin, laminin, and hyaluronic acid, which provide support for the recipient patient's cells. It has been demonstrated that acellular matrices undergo neo-vascularization and recellularization by host cells (19-21). In breast reconstruction, ADMs are used to enhance skin coverage, particularly after the placement of a silicone implant or tissue expander (4,22). Another goal is to reduce the risk of capsule contracture, a significant complication of implant-based surgeries, leading to a substantial decrease in the long-term cosmetic result (23). Some authors have described the risks associated with using ADMs, including infection rates, skin blisters, and overall complications (22,24). Some concerns were initially raised related to red breast syndromes found to be linked to ADMs by reconstructive surgeons (25,26). However, the probable bacterial origin of this syndrome has led to solutions improving the outcomes (27-29). As an interesting alternative, Gentile *et al.* described the use of titanium-coated polypropylene mesh in conservative mastectomies and pre-pectoral breast reconstruction (29). Their results showed better cosmetic outcomes when compared with tissue-expander-based techniques using the Breast-Q form.

A retrospective review conducted over ten years at the Massachusetts General Hospital included more than 3,000 patients undergoing breast reconstruction (4). One aspect of their analysis compared the outcomes of pre-pectoral implant reconstruction with ADM-enhanced coverage versus subpectoral techniques, where the implant is placed partially under the muscle. The study found a lower rate of nipple necrosis in the ADM group, with similar rates of infection, explantation, seroma, and overall reconstruction failure compared to the subpectoral group. Additionally, when comparing ADMs with synthetic mesh products, the study found higher complication rates with synthetic mesh. This highlights the advantages of using tissue-engineered biocompatible solutions instead of synthetic products. A study by Graziano *et al.* (30), based on the American Cancer Society database, focused on national outcomes of prepectoral breast reconstruction. They found that most (55%) of direct-to-implant reconstructions utilized ADM. Despite a slightly higher reoperation rate, the study reported a lower infection rate in the ADM cohort. However, regression analysis showed that caution should be exercised when using these scaffolds in patients with insulin diabetes, obesity, or active smokers. The significant limitations of this study were its retrospective design and short follow-up period of 30 days. The CARE trial (31), supported by Allergan (AbbVie, Chicago, IL, USA), is one of the first prospective studies with long-term follow-up. It revealed a twofold decrease in capsular contracture rates with ADM at the five-year mark and lower rates of implant malposition. These results were consistent in revision surgeries, highlighting the ability of ADMs to improve tissue health and provide stable, long-term outcomes. Forsberg *et al.* (32), followed by Ibrahim *et al.* (33) performed two interesting studies assessing the aesthetic outcome following tissue expander/implant-based breast reconstruction with and without ADMs. They found improvement in the overall aesthetic result, as well as in breast contour, implant placement, lower pole projection, and inframammary fold definition, as evaluated by five blinded plastic surgeons. The recent BROWSE multicenter study (34) carried out over a decade brought more evidence supporting improved aesthetic outcomes and reduced capsular contracture with prepectoral implant with ADM reconstruction compared to submuscular. The meticulous methodology, using the strongly validated BREAST-Q questionnaire (35), provides solid evidence supporting ADMs. Other authors have also supported these findings, emphasizing the advantages of ADMs in terms of safety (31,36), objective aesthetic outcomes (33), prevention of capsule contracture (31,33), and postoperative pain reduction.

Furthermore, the development of ADMs has facilitated the rise of prepectoral reconstructions, reducing the morbidity associated with subpectoral implant surgeries while maintaining safety and potentially improving aesthetic outcomes (32). Finally, while ADMs do add certain costs, de Blacam *et al.* (37) showed that single-stage implant procedures with ADMs are less expensive than tissue-expander-based approaches. On the other hand, as demonstrated by Bank *et al.* (38) in 2013, the use of ADM reduces the number of visits required for reconstructions with high-volume implants. A cost-effectiveness analysis by Jensen *et al.* demonstrated a positive impact of its use in breast reconstruction, which was confirmed by Krishnan *et al.* (39) found an increase in quality-adjusted life years.

Overall, ADMs have shown solid evidence as an optimal support for implant-based reconstructions, with excellent safety.

Improving fat grafting trophicity

Autologous fat grafting has several beneficial characteristics, including lack of immunogenicity, safe and simple procedure

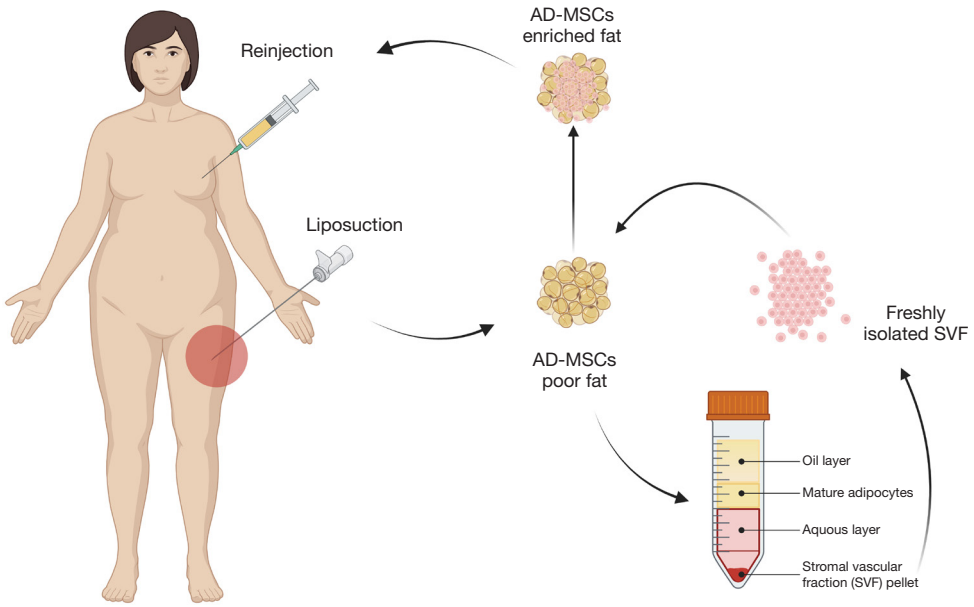

Figure 3 SVF-enriched fat transfer process. AD-MSC, adipose-derived mesenchymal stem cells; SVF, stromal vascular fraction.

with low complication rate and positive results, low cost, and easy usability (40-43). For this reason, fat grafting has become a standard of care in breast reconstruction for patients who do not wish to go through a complex surgery such as flap reconstruction or are reluctant to the idea of a foreign material such as a breast implant. Fat grafting has shown excellent natural cosmetic results when compared with implant-based breast lifting (41,42). If implant-based solutions provide immediate results with long-term volume preservation, some authors emphasized more natural aesthetic results with fat transfer (43). However, the volume loss after fat grafting is a significant issue, with a 30% to 40% loss of the initially grafted volume, according to the authors (44,45). Different solutions to improve fat survival have emerged thanks to recent bioengineering advances.

The first approach consists of platelet-rich plasma (PRP) enrichment. Some studies have suggested the addition of autologous PRP to the lipoaspirate. PRP is obtained from peripheral vein blood placed in sodium citrate anticoagulant and centrifugated (46,47). This process separates the red blood cells from the plasma, containing most (>90%) platelets. The obtained PRP is a natural reservoir of growth factors stimulating tissue repair and regeneration. It can be directly added to the lipoaspirate without any preconditioning, offering the advantage of a simple and cost-effective method. Animal models (48-51) first showed that the fat graft survival rate was significantly increased by adding PRP. Clinical studies start confirming these results: Gentile *et al.* (52) showed 69% graft retention when combining fat with PRP, which was significantly higher than fat grafting alone (39%) in their series of 50 patients. Several studies have been conducted on face treatment using fat transfer, showing similarly positive results (53-55). Finally, using endothelial cells has shown excellent results in preclinical models for enhancing fat grafting survivability (56).

A second approach uses the stromal vascular fraction (SVF) and adipose-derived mesenchymal stromal (or stem) cells (*Figure 3*). The initial isolated fat tissue is composed of adipocytes and stromal vascular fraction cells, which act as a cellular matrix and are composed of adipose stromal cells, preadipocytes, fibroblasts, vascular endothelial cells, muscle cells, pericytes, and a variety of immune cells (57). Most fat grafts' regenerative capacity is attributed to adipose-derived mesenchymal stem cells (AD-MSCs) in SVF (58). Several studies in the past decade have shown that stromal vascular fraction cells and adipose stem cells improve fat graft survival through both angiogenic properties and growth factor production (59-63). Recent biotechnological developments offer the possibility to engineer the fat and enrich it with SVF (61). Several protocols exist aiming to isolate this fraction (62,63). The standard enzymatic method consists of digesting the lipoaspirate by a collagenase, followed by centrifugation to obtain a pellet at the bottom of the tube, containing the

high-density adipose tissue (59). Other methods include spectroscopy or mechanical nano-fat techniques (oily liquid obtained after several steps of emulsification and filtration) (63-66). *In vitro* analyses emphasized filtration as a highly efficient mechanical technique for preserving the cell structures, while *in vivo* evidence seems to provide more promising results with enzymatic digestion (63,65). A prospective study compared the outcomes between several commercialized systems and found significant improvement with both enzymatic and mechanical-based systems (66). Enrichment with SVF, therefore, improves fat grafting by providing a bioengineered scaffold through cellular suspensions. Some studies have also suggested that SVF can lead to endothelial cell growth both *in vitro* and *in vivo*, enhancing the revascularization of fat grafts (67). However, to date, no formal proof of the differentiation of AD-MSCs into endothelial cells has been described, and endothelial progenitors contained in the SVF could be a likely explanation. One group more specifically tested human mononuclear cells containing endothelial progenitor cells and demonstrated increased fat graft survival in a rodent model (68). Overall, a safer approach is to consider the angiogenic potential of SVF cells as a whole through endothelial progenitors, AD-MSCs paracrine angiogenic activity, and potential AD-MSCs differentiation into endothelial cells. Further studies could focus more specifically on using human endothelial cells to enhance fat grafting survivability.

Clinical results with these techniques have already shown improved soft tissue volume maintenance and skin quality for scar repair and wound healing (64). In breast cancer reconstruction, SVF-enhanced autologous fat grafts present significantly better postoperative outcomes and contour maintenance at 1-year follow-up (58). However, the potential for an increased risk of breast cancer after injecting stem cells lacked adequate evidence for a long time. Mazur *et al.* (69) compared patients undergoing breast augmentation using SVF-enhanced lipofilling following a mastectomy or lumpectomy with patients not undergoing reconstruction. They matched both groups and showed no statistically significant difference in cancer recurrence after three years. The recurrence rate of the SVF group was even slightly lower (3.7% versus 4.13%) than the control group. Similarly, Calabrese *et al.* (70) prospectively compared conventional fat transfer and SVF-enhanced fat transfer in breast cancer patients. They had 40 to 60 patients in each of the fat grafting, SVF-enhanced fat grafting, and no reconstruction (control) groups, and the follow-up was 5 years. Again, they showed no difference between groups and a slightly lower recurrence in the SVF-enhanced group than in conventional fat grafting. Bielli *et al.* greatly reviewed the literature on this topic (71), highlighting the safety of adipose-derived stromal cell (ASC) and SVF enrichment of fat grafting with no significant change in the prognosis. They also performed a systematic review confirming these findings by emphasizing autologous fat grafting safety with no increased local-regional recurrences and no decreased disease-free survival (72). They also brought to light the poor amount of Level 1 evidence studies, such as international multicenter randomized studies, which should be promoted. In addition, it has been shown that magnetic resonance imaging allows for post-lipofilling breast monitoring, with experienced radiologists being able to distinguish malignant alterations from fat-related changes if patients are checked regularly (73).

An innovative study conducted in Italy in 2012 (74) compared 3D volume and contour maintenance following SVF- and PRP-enhanced fat grafting, with classic fat transfer as a control. Interestingly, they showed a similar enhancement of fat survival with 63% and 69% of volume maintenance after 1 year with SVF and PRP, respectively.

Another angle to approach fat grafting survivability enhancement is towards using bio-protectant molecules. William Austen Jr. and his team published in 2011 impressive results in a preclinical study while testing several poloxamer molecules on fat grafting (75). Poloxamers are triblock copolymers composed of polyoxyethylene (PEO) and polyoxypropylene (PPO) segments in different proportions. One of the poloxamers, specifically poloxamer 188 (P188), is considered highly promising for plastic surgery due to its ability to repair cell membranes and other beneficial biological characteristics (76-78). The initial hypothesis was that it is possible to improve cell survival by repairing membrane damage created during fat harvesting, reducing apoptosis in the days following grafting. It has been previously demonstrated that volume maintenance was improved by gentle manipulation of the fat (79). This team from the Massachusetts General Hospital showed that grafts treated with P188 exhibited a 50 percent decrease in apoptosis compared to the saline-treated controls and achieved a remarkable 72 percent weight-based survival after 6 weeks. These results are confirmed by another study (80), assessing DNA contents using PicoGreen analyses, which showed higher fat survivability with P188. These findings led to the development of fat-processing systems (Vitality, SIENTRA, Irvine, CA, USA), with ongoing multicenter studies to clinically confirm

these excellent results. Their preliminary results in the 13 enrolled centers show more than 86% retention after 6 months (81) needs to be confirmed at further time points. Another team (82,83) used this P188-based system to assess fat concentration and showed higher adipose volume (89%) when compared with other systems using a conventional Ringer rinsing solution. This approach could lead to better results in volume retention following fat grafting, eventually avoiding implant-based reconstructions and their complications.

It is worth noting that the legislative regulations need to evolve accordingly to some of these advances. Raposio and Ciliberti (83) highlighted that, according to the European Medicines Agency (EMA), ASCs are not classified as advanced therapy medicinal products if they have not undergone substantial manipulation, and their mode of action is considered homologous to the donor fat tissue, contributing to tissue renewal and turnover in the subcutaneous tissue. In contrast, substantial manipulations, such as collagenase digestion and cell culturing, are not allowed for ASCs to maintain their non-advanced therapy status. To date, only non-manipulated ASCs can be transplanted into the same anatomical or histological environment to be considered homologous. It is clear that ongoing studies need to show strong evidence before leading to changes in these regulations.

Building breast volume and shape through bio-printing

Breast volume and shape restoration is a critical stage in the breast reconstruction process. Traditionally, this is accomplished using silicone implants or autologous tissue transfers, either free or pedicled flaps, or fat grafting. Implant-based reconstructions offer several advantages, including immediate results, relatively simpler procedures, and shorter recovery times for patients; autologous flaps provide the opportunity to reconstruct both the soft tissue envelope and the breast volume, often resulting in superior long-term outcomes compared to silicone implants (84,85). However, both techniques have inherent drawbacks, which create a need to develop new perspectives in breast reconstruction. Fat grafting can recreate breast mechanical properties that closely resemble those of a natural breast. Nevertheless, there are instances where fat grafting alone may be insufficient, leading to inadequate volume or inadequate projection of the reconstructed breast mound due to the absence of three-dimensional structural support and resorption (86). Tissue engineering teams have tried to address this issue. This led to the development of 3D-printed scaffolds that could potentially provide the needed structural support and avoid resorption.

Tissue printing is an old concept. The first 3D patent was granted in 1986, and the first description of bioprinting was in 2003 (87). Later, in 2011, Melchels *et al.* introduced 3D printing in breast reconstruction (88). These groundbreaking works paved the way for developing 3D bio-printed implants in breast surgery. This innovative approach holds promise in combining the benefits of both implant-based reconstruction and autologous reconstruction. An advantage of 3D printing is the potential to tailor-print a resorbable implant to match the size of a defect, in the particular case of breast-conservative tumor removal. Magnetic resonance imaging can indeed precisely match the implant to the expected defect before surgery, enabling genuinely personalized manufacturing (89). Additionally, the versatility of materials available, including commonly used ones such as polycaprolactone (PCL), polylactic acid (PLA), and poly(lactic-co-glycolic acid) (PLGA), along with the potential to incorporate cell-loaded bio-inks, opens up limitless possibilities for implant creation.

The scaffold-guided approach aims to implant a scaffold that can effectively guide patient tissue ingrowth (*Figure 4*). While this approach shows promise, first-generation implants have primarily shown the formation of fibrous tissue with an unnatural hard texture (90,91). However, creating a flexible structure and adding adipose-derived stem cells (ADSCs) to the construct allowed for enhancing this process and improving the outcomes (92). Moreover, optimizing the placement of cells within the scaffold can further improve engraftment and leverage the structural possibilities offered by 3D printing, combined with the tissue regeneration properties of fat grafting. Chhaya *et al.* demonstrated that delayed fat grafting two weeks post-implantation promotes angiogenesis and adipose tissue regeneration, allowing for the generation of large volumes of adipose tissue in a preclinical model (93).

Mohseni *et al.* refined this technique. They developed a modular construct comprising an external layer for structural support and internal content that enhances fat grafting (94). However, two main challenges are associated with this approach. The first is achieving proper scaffold vascularization to ensure successful fat engraftment. The second challenge involves effectively managing the scaffold's resorption phase and addressing the construct's transient properties, which should mimic native breast tissue (95,96). Alternative methods involving bio-regenerative fillers composed of collagen have been proposed as potential

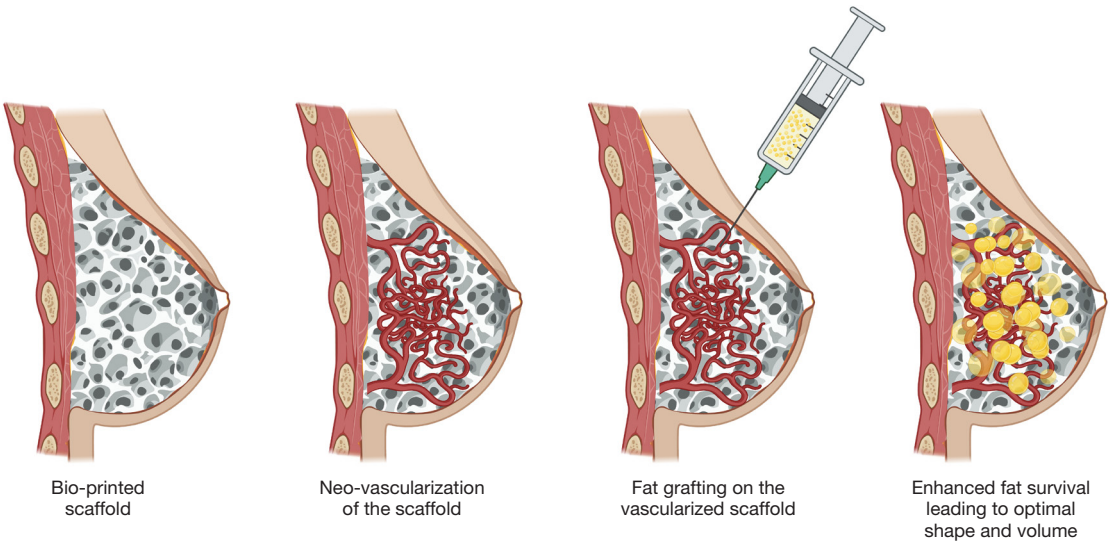

Figure 4 Concept of 3D and 4D bio-printed scaffolds as a recipient structure for fat grafting, improving overall survival and volume and shape retention.

solutions (97). Bio regenerative filling may serve as an alternative to a complete scaffold, particularly in oncologic breast conservative surgery cases.

The concept of a resorbable 3D printed structure has also let to the development of tissue engineering chambers (TECs). Morrison *et al.* first clinically tested this concept in Australia in 2016 (98). Their TEC involved an acrylic, perforated dome-shaped chamber that creates a dead space in which a pedicled fat flap is placed. The rest of the cavity is progressively filled with a seroma, ultimately leading to flap hypertrophy, providing volume. One major drawback of this method is the unnatural appearance of the breast due to the non-resorbable implant that requires a follow-up procedure for removal. More recently, Lattice Medical (Loos, France) improved this aspect by developing a bio-absorbable implant [Mat(T)isse] that fully degrades within 12 months, allowing for a one-stage surgical protocol (99-101). This implant is currently undergoing a clinical trial in Europe and has so far shown promising results. Another brand (Bellaseno GmbH, Leipzig, Germany) is working on a similar project and has manufactured a resorbable scaffold (Senella PCL Breast Scaffold) made of PCL that degrades in 24 to 36 months. This scaffolding is intended for both breast augmentation and reconstruction (102).

The concept of 4D printing introduces a new level of complexity and opens exciting possibilities in manufacturing implants. With 4D printing, implants can have characteristics that evolve over time, adapting to the patient's body's mechanical, physical, or enzymatic constraints (103). This advancement allows for better control over the resorption of biomaterials, transforming it into an opportunity to shape and modify the implant's properties as needed. While still in its early stages, 4D printing holds immense potential for expanding the range of possibilities in implant technology. Furthermore, 4D printing enables the inclusion of drugs on the scaffold, facilitating local delivery for long-lasting and controlled diffusion (104). This feature can be used to achieve antitumoral effects (105-108) and even prevent post-operative complications such as thrombosis or infection (109).

Several authors have conducted research on animal models to explore the possibility of incorporating cells directly into 3D-printed breast structures. For example, human umbilical vein endothelial cells (HUVECs) (110) and human adipose-derived stromal cells (hADSCs) (111) have been investigated. Using bio-inks composed of hydrogels loaded with cells appears to be a promising approach, as it has demonstrated high cell survival rates (112). In a study by Sokol *et al.*, primary human breast cells were successfully isolated and incorporated into a hydrogel, resulting in the regeneration of functional breast tissue (113). This tissue exhibited hormone responsiveness and was able to generate lipid droplets. Integrating cells directly into the bionic structure offers several advantages, such as accelerating adipose tissue regeneration and enhancing the adipose and vascular content of the reconstructed breast. However, current approaches have been restricted to animal testing. This

limitation is partly due to potential concerns regarding the inclusion of cells in the bionic structure, as it may increase the risk of cancer recurrence. Before clinical applications can be implemented, it is crucial to assess the oncological safety of this approach, particularly for oncologic reconstruction (114).

NAC engineered reconstructions

Nipple reconstruction is a crucial component of breast reconstruction, as it significantly influences patient satisfaction with the overall outcome (115). The natural appearance of the NAC is of utmost importance (116), with factors such as position, color, projection, and texture playing a significant role. While autologous techniques are commonly used for nipple reconstruction, they may not always meet patients' specific needs in the long term (117-124). Surgeons have attempted various approaches to restore the NAC's natural appearance, including 3D tattoos, autologous skin or mucosal grafts, and local flaps. However, the absence of a consensus on a gold standard technique among the multitude of autologous approaches underscores the necessity for further advancements in the field. Thus, a growing body of literature has focused on innovative strategies for reconstructing the NAC, offering promising advancements in achieving a natural and aesthetically pleasing outcome. This summary outlines the key trends in this field.

Local flap nipple reconstruction is usually associated with a cartilage graft, including autologous (125), or banked costal cartilage (126), in order to improve the structural support of the nipple. However, these grafts often come with drawbacks such as donor site morbidity (if autologous) and resorption, which can lead to long-term nipple projection loss. To address these issues, biomaterials have been explored as potential solutions. Acellular dermal matrix (127-129), calcium hydroxyapatite (130,131), lyophilized allogenic costal cartilage (132), and biological collagen implants (133,134) have garnered significant interest as potential options in this regard. However, their cost and lack of long-term support are often perceived as limitations to their utilization. Injectables, increasingly favored by surgeons for their convenience in outpatient settings, have also been gaining popularity. Among them, hyaluronic acid (135,136), and biomaterials derived from bovine collagen (137) present exciting alternatives to retro-areolar fat grafting.

Synthetic materials with adequate biocompatibility, such as silicone and polytetrafluoroethylene (PTFE) (138), have been explored for ready-to-use and long-lasting internal NAC prosthetics. Jankau *et al.* reported high complication rates with frequent (if not systematic) local necrosis and implant extrusion after experimenting with implantable silicone rods (139). This may be attributed to the heightened pressure exerted by the silicone rod on the flap used for breast reconstruction. FixNip NRI (FixNip LTD, Caesarea, Israel) is a silicone flexible Nipple reconstruction implant (NRI) approved for sale in Europe and currently under FDA review. Its internal Nitinol frame allows for a flexible yet reliable and long-lasting reconstruction of the NAC in a surgical-friendly manner (140). Although this implant also carries the risk of infection and extrusion, it has not proven to be problematic.

Another notable trend is the use of 3D printing technology. Several techniques already discussed in the previous section (3.3) can be applied to NAC engineering and imply either printing a resorbable scaffold or directly bio-printing cell-containing inks. The synergistic blend of scalability and production efficiency, combined with the inherent capacity to retain flexibility for customization, confers significant advantages when considering industrial production. Vernice *et al.* described a 3D-printed PLA scaffold with an ovine decellularised infill (141), while Samadi *et al.* opted for a costal cartilage fill (142). Similarly, Dong *et al.* report using a 3D printed poly-4-hydroxybutyrate (P4HB) that is a fully resorbable FDA-cleared biomaterial to construct scaffolds filled with processed costal cartilage (143). With these techniques, nipple projection was maintained over time with natural biomechanics properties. In cell-containing bio-inks techniques, ADSCs offer the hypothetical possibility of combining the structural benefits of the 3D printed scaffold with the regenerative properties of the ADSCs. This theoretical advantage needs to be weighed against the inherent limitation of these constructs, as they lack cellular differentiations necessary for optimal structural function (144). An alternative approach could be using bio incubators to facilitate cell maturation and the subsequent implantation of differentiated tissue. However, regardless of the technique employed, autologous cell seeding into the scaffold proves to be a costly solution, and the resulting implant is not readily deployable, thereby limiting the practicality of this approach, according to certain authors.

With the advent of decellularization bioengineering techniques (143,144), exciting advancements have been made in developing NAC scaffolds for tissue regeneration.

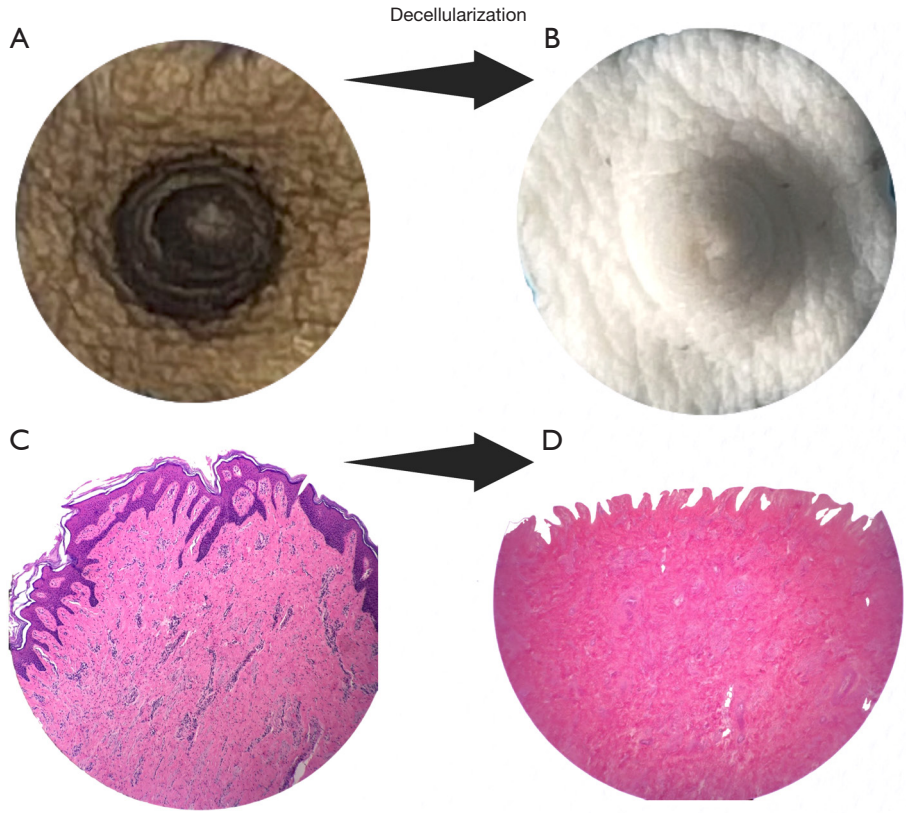

Figure 5 Decellularization of porcine nipples. The native nipples were freshly harvested from Yucatan minipigs (A,C), and decellularization (B,D) was performed using our published protocol (145). (C,D) Light microscopy, hematoxylin and eosin staining, ×10.

These innovative technologies, such as ADMs, have been proven safe and are commercially available, finding widespread clinical applications. Numerous studies have demonstrated that acellular nipple scaffolds (ANS) are free from cellular antigens and effectively cleared of DNA (145), using the same threshold of 50 ng/mg of tissue, thereby minimizing the risk of rejection by the recipient's immune system. Moreover, these scaffolds maintain the integrity and bioactivity of the extracellular matrix, enabling successful reseeding with cells (146,147). They have also shown the capacity to support host-mediated re-cellularization with the growth of epithelial cells, neo-vasculature, and even nerve ingrowth (148). While proof of concept has been achieved using non-human-primate-derived ANS (149), concerns regarding ethics, cost, and limited availability have prompted our team to explore porcine-originated scaffolds with promising results (*Figure 5*), either as a preclinical model or as a genuine source of ANS (145). Re-cellularization with autologous cells can further enhance the outcomes of bioengineered nipple grafts. This approach allows for better control over scaffold contracture and facilitates quicker integration in the recipient, thereby achieving a fully tolerated and successful bioengineered nipple graft. Our team is actively investigating this exciting avenue to eventually achieve a perfect match between the scaffold and the recipient.

Strengths and limitations

Our article demonstrates strength in providing a broad and accessible insight into the current landscape and future prospects of tissue engineering applied to breast reconstruction. It discusses a range of techniques, from stem cells and scaffolds to 3D bioprinting, using a comprehensive, yet understandable style. However, the inherent limitations of the narrative review format are apparent, including potential bias due to its non-systematic nature, and the absence of in-depth discussion of the different topics. Additionally, the speculations on future advancements, although intriguing, remain mostly

hypothetical due to the rapidly evolving nature of this field.

Conclusions

Tissue and Bio- engineering represent a promising approach for breast reconstruction. These innovative approaches can eventually address multiple steps of the complex process of breast reconstruction. An asymmetrical evolution is certain, with some processes already in use while others are in the early stages of development. Combination with autologous techniques can help reach the expected results, which are a complete, precise and stable restoration of the reconstructed breast's appearance, as well as its functional impact as a part of women's femininity.

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Footnote

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