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Review Article

Revolutionizing Breast Cancer Treatment: The Role of Regenerative Medicine

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ABSTRACT

Breast cancer remains the most prevalent cancer among women worldwide. Although conventional treatments such as chemotherapy, radiotherapy, and surgery have significantly improved survival, they are often limited by tumor heterogeneity, immune escape, and the lack of personalized post-surgical reconstruction. This review explores the intersection of regenerative medicine and immunotherapy as a novel strategy in breast cancer management. Natural killer (NK) cell therapies, including chimeric antigen receptor (CAR)-NK platforms, offer promising anti-tumor activity with lower toxicity compared to CAR-T cells. Artificial intelligence (AI) is accelerating the development of these therapies by identifying predictive biomarkers and optimizing CAR design. Mesenchymal stem cells (MSCs), known for their regenerative and immunomodulatory properties, are being investigated for both systemic anti-cancer therapy and localized tissue repair. The use of MSC-derived extracellular vesicles (EVs) further enhances therapeutic safety while preserving efficacy. Scaffold-based tissue engineering plays a critical role in breast reconstruction, providing a structural matrix that supports vascularization and cell integration. We also examine translational challenges, including variability in patient immune profiles, manufacturing scalability, and regulatory compliance. By integrating cell-based immunotherapy, stem cell biology, biomaterials, and AI-driven precision tools, the field is moving toward a more personalized and restorative model of breast cancer care. Continued interdisciplinary collaboration will be essential to overcome remaining barriers and fully realize the clinical potential of these emerging therapies.

Key words: Breast cancer, NK cells, Mesenchymal stem cells (MSCs), Immunotherapy, Tissue engineering, Personalized medicine

INTRODUCTION

Breast cancer remains the most commonly diagnosed cancer among women globally, with over 2.3 million new cases and 685,000 deaths reported in 2020. By 2040, the incidence is projected to surpass 3 million annually, with mortality nearing 1 million cases [1]. This growing burden disproportionately affects low- and middle-income countries (LMICs), where limited access to screening, late-stage presentation, and inadequate treatment infrastructure contribute to poor outcomes [2,3]. In countries such as Malaysia and Thailand, breast cancer accounts for over one-third of new female cancer diagnoses, with survival rates undermined by diagnostic delays and socioeconomic barriers.

Conventional treatment modalities, including surgery, radiotherapy, chemotherapy, hormone therapy, and targeted agents, have improved outcomes but are often limited by adverse effects, treatment resistance, and poor long-term quality of life. For instance, up to 30% of hormone receptor-positive breast cancers eventually develop resistance to endocrine therapy, requiring alternative or combination strategies [4]. These limitations have driven growing interest in integrating regenerative medicine and immunotherapy into standard breast cancer care.

Among emerging immunotherapies, natural killer (NK) cell-based therapy has attracted significant attention for its ability to selectively kill tumor cells without the need for antigen presentation. In parallel, genetically engineered mesenchymal stem cells (MSCs) are being investigated for their tumor-homing capabilities, immunomodulatory properties, and dual potential to deliver anti-cancer payloads while promoting post-mastectomy tissue regeneration [5,6]. These therapies, particularly when integrated, represent a novel approach to eradicate residual disease and simultaneously repair damaged tissue.

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Despite promising preclinical data, several challenges hinder clinical translation. These include MSC-related safety concerns (*e.g.*, the potential for tumor promotion in certain microenvironments), regulatory complexity surrounding genetically modified cells, and difficulties in large-scale manufacturing and cost containment [7,8]. Likewise, NK cell therapies face barriers such as short *in vivo* persistence and suppression within the tumor microenvironment, which reduce their therapeutic impact in solid tumors [9]. While ongoing Phase I/II trials, such as NCT04220676 using CAR-NK cells for metastatic breast cancer, demonstrate feasibility, reproducible efficacy in heterogeneous patient populations remains a major hurdle.

In parallel, tissue engineering technologies, such as 3D-printed scaffolds, decellularized matrices, and prevascularized constructs, are advancing post-mastectomy breast reconstruction. These innovations aim to improve not only cosmetic outcomes but also the long-term viability of reconstructed tissue. However, their success depends on overcoming key issues such as vascularization, biocompatibility, and cost-effectiveness [10,11].

This narrative review synthesizes current advances in regenerative medicine for breast cancer treatment, focusing on three key domains: (1) NK cell immunotherapy, (2) MSC-based gene and cell therapies, and (3) tissue-engineered reconstruction. We examine the mechanisms, limitations, and translational potential of each approach, while highlighting synergistic strategies that bridge tumor eradication with regenerative repair. We also explore how artificial intelligence (AI), multi-omics analysis, and biomarker discovery are enabling personalized therapeutic strategies that may overcome tumor heterogeneity and improve response prediction [12]. Finally, we identify research gaps and regulatory bottlenecks that must be addressed to accelerate the clinical adoption of these integrative, next-generation therapies.

NATURAL KILLER (NK) CELLS FOR BREAST CANCER IMMUNOTHERAPY

Introduction to NK Cells in Cancer Immunotherapy

Natural killer (NK) cells are cytotoxic lymphocytes of the innate immune system that exert antitumor activity through the recognition of stress ligands on transformed cells without prior sensitization. Unlike T cells, NK cells rely on a balance of activating and inhibitory receptors to discriminate between healthy and malignant cells. Once activated, NK cells release perforin, granzymes, and engage death receptors such as FasL and TRAIL to induce apoptosis in target cells [13,14]. In breast cancer, particularly in immunologically "cold" subtypes such as luminal A, NK cells face suppression from the tumor microenvironment (TME), which is rich in immunosuppressive cytokines such as TGF-β, IL-10, and PGE2. These signals downregulate NK-activating receptors like NKG2D and impair their infiltration and cytotoxic function [5].

Clinical Applications and Comparative Context

Multiple therapeutic strategies have been developed to harness NK cells in breast cancer, including adoptive transfer of expanded NK cells, chimeric antigen receptor-engineered NK cells (CAR-NK), and bispecific/trispecific NK cell engagers. Among these, CAR-NK cells are particularly promising, combining the tumor specificity of CAR-T cells with reduced risk of cytokine release syndrome and graft-versus-host disease (GVHD). In the Phase I/II trial (NCT04220676), HER2-targeted CAR-NK cells demonstrated early signs of clinical activity in patients with metastatic breast cancer, with a favorable safety profile. However, in comparison to CAR-T therapy, which has shown dramatic effects in hematologic malignancies, CAR-NK therapies for solid tumors face additional barriers, including limited *in vivo* persistence and challenges in trafficking to tumor sites.

Compared to mesenchymal stem cell (MSC)-based therapies, NK cell-based immunotherapy offers a more direct cytotoxic effect but lacks the regenerative potential and immunomodulatory capacity of MSCs. Nevertheless, NK cells are faster acting and do not require prior priming. The therapeutic advantages of each platform suggest a synergistic potential, particularly in combining MSCs engineered to modulate the TME or secrete NK-stimulatory cytokines.

Barriers and Challenges in Clinical Translation

Despite advances, several hurdles limit the clinical success of NK cell therapy. The immunosuppressive TME is a significant barrier, as factors like TGF-β and IL-10 inhibit NK cell recruitment, cytokine release, and receptor activation. Moreover, the hypoxic and fibrotic nature of many breast tumors creates a hostile environment that limits NK cell infiltration and survival. Unlike CAR-T cells, NK cells

have short half-lives post-infusion and require cytokine support (*e.g.*, IL-15 or IL-2) to sustain activity. ALT-803, an IL-15 superagonist, is currently under clinical evaluation for enhancing NK persistence.
CAR-NK cells are a promising cellular immunotherapy for cancer. Patient heterogeneity, such as differences in tumor antigen expression (*e.g.*, HER2, MUC1), HLA genotype, and immune checkpoint ligand density, can dramatically impact CAR-NK efficacy[5,15]. These factors influence target recognition, persistence, and immune escape, contributing to variability in clinical outcomes.
Another translational barrier is manufacturing scalability. Unlike conventional pharmaceuticals, NK cell therapies must be produced under Good Manufacturing Practice (GMP) conditions, with strict batch-to-batch consistency. Autologous NK cells present challenges of variable quality and limited expansion, while allogeneic sources raise concerns about immune compatibility. The production cost of NK therapies remains high, with limited automation and regulatory complexity slowing commercialization.

Personalized Strategies, Biomarkers, and Artificial Intelligence

Personalizing NK therapy requires a better understanding of predictive biomarkers. Tumor HLA class I expression plays a pivotal role in regulating NK cell activity via inhibitory KIR receptors; tumors with low HLA-I expression are more susceptible to NK-mediated lysis. Additionally, the presence of activating ligands (*e.g.*, MICA/B, ULBPs) for receptors like NKG2D correlates with better outcomes. Recent studies also suggest that stromal expression of CXCL9/10, which recruits $CXCR3^{+}$ NK cells, could be used as a predictive indicator of NK cell infiltration.
AI is transforming NK cell therapy by enabling the identification of such biomarker signatures through high-throughput multi-omics data analysis. For example, AI-driven algorithms have been used to stratify triple-negative breast cancer (TNBC) patients based on NK gene expression profiles, improving patient selection and treatment matching[12]. Additionally, machine learning models are aiding in optimizing CAR designs and predicting potential off-target toxicities by simulating ligand–receptor interactions before preclinical testing. Recent work has applied convolutional neural networks (CNNs) to classify histopathological images and predict NK cell infiltration in breast tumors, improving immune landscape profiling[16,17]. Support vector machines (SVMs) and random forest models have also been trained on transcriptomic and single-cell RNA-seq data to identify NK-sensitive tumor subtypes and stratify patients likely to benefit from CAR-NK therapies[18,19]. These algorithms enhance patient selection and make preclinical testing more targeted and efficient.

Future Integration and Synergistic Approaches

Looking forward, the most promising strategies involve combining NK cells with complementary approaches that overcome the limitations of monotherapy. For instance, immune checkpoint inhibitors such as anti-TGF-β or anti-PD-L1 antibodies can be used to reverse TME-mediated suppression. Gene-editing tools like CRISPR/Cas9 are being employed to delete inhibitory receptors or insert cytokine-supportive genes into NK cells, thereby improving their survival and tumor-killing potential. Additionally, metabolic reprogramming targeting pathways such as mTOR or glycolysis may enhance NK function under nutrient-deprived conditions within the TME.
Critically, synergy between NK cells and MSCs is an emerging frontier. MSCs can be engineered to secrete IL-15 or other NK-activating cytokines locally within the TME, enhancing NK infiltration and cytotoxicity without systemic toxicity. Furthermore, MSCs may be used as delivery vehicles for NK-engaging molecules, bridging innate immunity and tissue repair. This dual-modality approach could transform post-surgical management of breast cancer by simultaneously addressing residual tumor burden and promoting tissue regeneration, a concept explored further in the next section.

GENETICALLY MODIFIED MESENCHYMAL STEM CELLS (MSCS) IN BREAST CANCER THERAPY AND REGENERATIVE MEDICINE

Introduction to MSCs in Breast Cancer

Mesenchymal stem cells (MSCs) are multipotent stromal cells capable of differentiating into osteoblasts, chondrocytes, and adipocytes. Their tumor-homing ability, immunomodulatory functions, and low immunogenicity make them attractive for cancer therapy and regenerative medicine

applications. In breast cancer, MSCs have been investigated for their dual utility: as therapeutic vehicles for targeted anti-tumor delivery and as facilitators of soft tissue regeneration following mastectomy[20]. These cells can migrate to sites of inflammation and tumor activity, enabling site-specific delivery of therapeutic agents with reduced systemic toxicity.

Genetic Modification for Enhanced Therapeutic Efficacy

Genetic engineering of MSCs is a key strategy to enhance their therapeutic specificity and efficacy. For example, Liu *et al.* (2018) demonstrated that MSCs engineered to express interleukin-18 (IL-18) significantly suppressed tumor growth in a murine model of breast cancer by enhancing local immune activation and reducing angiogenesis[21]. Similarly, MSCs engineered to express the suicide gene cytosine deaminase (CD) can convert the prodrug 5-fluorocytosine into the chemotherapeutic agent 5-fluorouracil (5-FU), leading to localized cytotoxicity in the tumor microenvironment while minimizing systemic toxicity[22]. These genetic modifications allow MSCs to act as "smart" delivery platforms for targeted cancer therapy.

Safety Concerns and Mitigation Strategies

Despite their promise, the use of MSCs in oncology raises safety concerns, particularly regarding their potential to support tumor growth, metastasis, or immune evasion under certain conditions. Some studies have reported pro-tumorigenic effects of MSCs, including secretion of growth-promoting factors and immune-suppressive cytokines. To address these risks, several safety engineering strategies have been proposed. One approach involves integrating suicide gene systems into MSCs, such as inducible caspase-9 (iCasp9), which can be pharmacologically activated to eliminate MSCs *in vivo* if adverse effects occur[23]. Additionally, preconditioning MSCs with cytokines or modifying their culture conditions can promote an anti-tumorigenic phenotype. Another emerging strategy is to use extracellular vesicles (EVs) derived from engineered MSCs instead of whole cells to mitigate risks associated with cell proliferation and transformation.

Clinical Translation: Challenges and Early Trials

The clinical translation of genetically modified MSC therapy in breast cancer is still at an early stage. A Phase I clinical trial (NCT02807805) investigated the safety of MSCs expressing interferon-beta in patients with advanced solid tumors, including breast cancer. The trial demonstrated that the therapy was well-tolerated with no dose-limiting toxicities, although therapeutic efficacy was modest, highlighting the need for optimization in delivery, persistence, and tumor targeting (ClinicalTrials.gov, 2024). Translational challenges also include variability in MSC function across donors, difficulty in large-scale expansion under Good Manufacturing Practice (GMP) conditions, and complex regulatory oversight due to the use of genetically modified cells.

Integration with Artificial Intelligence and Omics Technologies

Artificial intelligence (AI) and omics technologies are increasingly being used to optimize MSC-based therapies. Transcriptomic and proteomic profiling of MSCs can identify subpopulations with enhanced tumor-homing or immunomodulatory potential. AI algorithms trained on secretome or surface marker data can predict therapeutic potency and assist in donor screening, bioprocess optimization, and batch quality control[20]. Integration of such tools into the MSC manufacturing pipeline offers opportunities to reduce variability, improve clinical predictability, and streamline regulatory compliance.

MSC–NK Cell Synergy: A New Therapeutic Paradigm

Recent studies suggest a promising synergy between MSCs and natural killer (NK) cells in the treatment of solid tumors. MSCs can be engineered to secrete cytokines such as IL-15 or IL-21, enhancing NK cell activation and infiltration into tumor sites. This combinatorial approach has shown superior tumor suppression in preclinical models compared to monotherapies[20]. Importantly, such an integrative strategy may provide dual therapeutic benefits, targeting residual cancer cells via NK cells and promoting post-surgical soft tissue repair through MSC-mediated regeneration.

BREAST RECONSTRUCTION AND CLINICAL TRANSLATION OF MSC-BASED THERAPIES

Breast reconstruction is a critical aspect of breast cancer survivorship care, offering patients the opportunity to restore body image and psychological well-being post-mastectomy. Traditional reconstructive strategies include implant-based and

autologous tissue techniques. While both have demonstrated clinical success, emerging regenerative strategies, particularly those involving MSCs and advanced scaffolds, are redefining what is possible in post-oncologic reconstruction.

Implant-Based vs. Autologous Approaches: Opportunities and Limitations

Implant-based reconstruction (IBR) remains the most commonly performed method due to shorter surgery time and hospital stay. Advances such as acellular dermal matrices (ADMs) have reduced capsular contracture and improved cosmetic outcomes. However, IBR is often contraindicated in patients receiving radiation therapy because of poor tissue quality and higher complication risks. Autologous reconstruction, using flaps like TRAM or DIEP, offers natural results and is better suited for irradiated patients. Yet, these procedures are resource-intensive, require microsurgical expertise, and are associated with donor-site morbidity. Additionally, volume loss and fat necrosis remain concerns even with successful flap transfer.

Fat Grafting and Stem Cell Integration

Fat grafting, commonly used as an adjunct to refine shape and contour, has gained attention for its regenerative potential. Adipose-derived stem cells (ADSCs) within lipoaspirates are thought to promote angiogenesis and improve fat graft survival. Clinical studies have shown that ADSC-enriched fat grafts can improve volume retention compared to standard fat grafting. However, concerns about ADSCs promoting tumor recurrence in the post-mastectomy setting persist. Trials such as RESTORE II (NCT01555654) and the ongoing SAFE-ASC trial are evaluating long-term oncologic safety. To mitigate risks, newer approaches are using ASC-derived EVs instead of live cells, showing reduced fibrosis and improved fat graft retention in irradiated models.

Scaffold-Based Tissue Engineering in Reconstruction

Tissue engineering has enabled the development of scaffolds that provide structural support and guide tissue regeneration. As summarized in **Table 1** and Supplementary **Table S1**, materials such as ADM, dECM, and GelMA show high compatibility with MSCs and support vascularization, both critical for sustained graft integration. For instance, decellularized adipose tissue scaffolds seeded with ADSCs have shown enhanced adipogenesis and angiogenesis in animal models. Clinical trials are now assessing bioengineered constructs with MSCs or ASCs to improve reconstructive outcomes (*e.g.*, NCT04892537). However, translating these materials into routine clinical use demands resolving challenges such as GMP-compliant production, immunogenicity control, and cost-effectiveness in low- and middle-income settings.

Among the various scaffolds explored for breast tissue engineering, natural materials such as acellular dermal matrices (ADMs), collagen, and decellularized extracellular matrices (dECMs) offer superior biocompatibility and vascularization potential—crucial for long-term graft survival and integration. ADMs, in particular, are already used clinically in implant-based breast reconstruction. In contrast, synthetic polymers like PLGA and PEG offer tunable mechanical and degradation properties but often require a combination with growth factors or cells to enhance angiogenesis. Natural hydrogels such as fibrin and silk fibroin also show promise due to their pro-angiogenic and cell-supportive environments, although their mechanical strength may be a limitation. The choice of scaffold depends heavily on the intended application—be it structural support, delivery of MSCs, or long-term regeneration. As detailed in **Supplementary Table S1**, specific scaffold–cell pairings such as ADSCs with decellularized adipose tissue (DAT) and GelMA hydrogels have shown robust adipogenic differentiation and angiogenesis *in vivo*. These findings directly inform clinical scaffold selection, especially for patients undergoing reconstruction post-radiation, where enhanced vascularization is needed to counter fibrosis and improve graft retention [30]. Such preclinical evidence provides a translational bridge toward selecting biomaterials tailored for patient-specific reconstruction challenges.

Clinical Trials and Translational Progress

Several early-phase trials have demonstrated the safety of MSC-based therapies in solid tumors, including breast cancer. In trial NCT02807805, IFN-β–secreting MSCs were administered to patients with metastatic cancers and showed no dose-limiting toxicity, although clinical efficacy was modest. Similarly, NCT05109929 is currently exploring MSC–NK cell co-therapies for their potential to modulate the immune microenvironment post-surgery. To transition from feasibility to routine use, MSC therapies must overcome donor heterogeneity, inconsistent potency, and safety concerns. Standardization of MSC manufacturing (*e.g.*, cytokine release profiles and differentiation assays) is a critical next step.

Table 1: Summary of scaffold classes relevant to breast tissue engineering, including material category, biodegradability, angiogenic and MSC compatibility potential, and current translational status. This overview helps contextualize the scaffolds' clinical applicability for breast reconstruction and cell-based regenerative strategies

Scaffold Material	Source/Type	Biodegradability	Vascularization Potential	MSC Compatibility	Preclinical/Clinical Use	References
Acellular Dermal Matrix (ADM)	Human/Porcine-derived	Slow	Moderate–High	High	Widely used clinically (*e.g.*, IBR)	[24]
Collagen	Natural (Type I)	Fast–Moderate	High	High	Used in preclinical breast models	[25]
PLGA	Synthetic polymer	Moderate	Low–Moderate	Moderate	Common in preclinical trials	[26]
PEG-based hydrogels	Synthetic	Slow (tunable)	Low–Moderate	Moderate–High	Emerging in preclinical systems	[27]
Fibrin	Natural (plasma-derived)	Fast	High	High	Used in wound healing; early studies	[28]
Decellularized ECM (dECM)	Tissue-derived	Moderate	High	High	Preclinical; promising tissue mimicry	[29]

Additionally, regulatory agencies like the FDA and EMA now require functional potency assays as part of investigational new drug applications.

Personalized and Integrated Reconstruction Strategies

With the convergence of imaging, AI, and 3D bioprinting, breast reconstruction is becoming increasingly individualized. Patient-specific scaffolds designed via CAD modeling can match anatomical contours and tissue volume more precisely than traditional methods. Ongoing studies aim to evaluate whether AI-optimized scaffold architectures improve fat retention and vascularization outcomes compared to conventional flaps. A truly personalized strategy may involve integrating prevascularized scaffold systems to enhance graft survival, acellular EV therapies to reduce fibrosis, and patient-specific imaging and omics data to tailor scaffold–cell combinations.

TRANSLATIONAL CHALLENGES AND CLINICAL TRIALS IN MSC-BASED BREAST RECONSTRUCTION

The path from preclinical innovation to clinical adoption in MSC-based breast reconstruction involves navigating complex translational barriers. Despite a strong mechanistic rationale and promising safety profiles, widespread integration into standard reconstructive workflows remains limited due to several factors.

Regulatory and Manufacturing Barriers

A major hurdle in clinical translation is the lack of standardized manufacturing protocols for MSCs. Variability in donor source, isolation techniques, and cell expansion introduces significant heterogeneity in therapeutic performance. Regulatory agencies such as the FDA and EMA now require validated potency assays, such as cytokine secretion profiles, immunosuppressive function (*e.g.*, IDO, TGF-β1), or angiogenic capacity, as part of MSC release criteria. Establishing GMP-compliant processes and quality control standards remains a priority before large-scale implementation.

Safety Concerns in Oncologic Settings

Concerns persist about the potential pro-tumorigenic effects of MSCs, particularly in the post-mastectomy bed, where dormant tumor cells may remain. While several studies report a lack of tumor-promoting behavior in immunocompetent models, data in irradiated or high-risk patients remain sparse. For instance, the RESTORE-2 trial (NCT01555654) evaluated ASC-enriched fat grafting in breast reconstruction and found no increase in

local recurrence over three years. Similarly, Lee *et al.* (2023) demonstrated that ASC-derived exosomes reduced radiation-induced fibrosis without stimulating tumor markers in preclinical models[31].

Clinical Trial Landscape and Current Status

Several early-phase clinical trials have evaluated MSC-based therapies in breast cancer patients. In NCT02807805, MSCs engineered to express interferon-β were administered systemically to patients with advanced solid tumors. While no dose-limiting toxicity was reported, antitumor efficacy was limited. The ongoing NCT05109929 trial is evaluating the co-administration of NK cells and MSCs in post-surgical breast cancer patients to assess safety and immunomodulatory outcomes. In the context of scaffold-assisted therapies, NCT04892537 is exploring the use of 3D-printed biodegradable scaffolds seeded with ADSCs to enhance volume retention and reduce fibrosis in autologous reconstruction. These trials highlight the clinical potential of MSC-based interventions but also the slow progression of such approaches due to regulatory, ethical, and technical complexities.

Future Trial Design Considerations

To move the field forward, future trials should incorporate standardized endpoints, such as long-term fat graft viability, fibrosis scoring, and oncologic surveillance over five or more years. Stratification of patients by prior radiation exposure, immune profile, and genetic risk may reveal responder subgroups. The use of acellular MSC-derived EVs may offer a regulatory and safety advantage over cell-based methods, particularly in high-risk populations. Multi-arm comparative trials—comparing standard autologous flap reconstruction, fat grafting, MSC-assisted scaffolds, and exosome-enriched therapies—are warranted to guide clinical best practices. As this translational pipeline matures, collaborative consortia among academic institutions, regulatory bodies, and industry partners will be essential to establish robust, safe, and scalable therapeutic platforms.

EMERGING DIRECTIONS AND RESEARCH PRIORITIES

The convergence of immunotherapy, regenerative medicine, and tissue engineering in breast cancer care opens new frontiers but also raises complex biological, clinical, and translational questions that remain unresolved.

Enhancing the Immunoregenerative Interface

Future research must address the interaction between therapeutic cells and the immunosuppressive tumor microenvironment (TME). While NK cells and MSCs show promise individually, their combined application remains poorly understood. Investigating how MSC-derived cytokines (*e.g.*, IL-15, IL-21) modulate NK cell persistence and cytotoxicity could uncover new therapeutic synergies. Moreover, fine-tuning this balance to avoid MSC-induced immune dampening in cancerous contexts will be critical[32].

Scaffold Optimization Beyond Mechanics

While materials science has focused on mechanical compliance and degradation kinetics, the next wave of scaffolds must incorporate biological intelligence: dynamic release of immunomodulators, spatially programmed angiogenesis, and responsiveness to inflammatory cues. Decellularized adipose tissue and ECM-mimetic hydrogels offer such potential, but comparative studies are needed to determine which materials best support long-term graft survival, especially in irradiated beds[33].

Safety and Standardization in Cellular Therapies

The clinical translation of MSC- or ASC-based strategies remains constrained by donor variability, potency uncertainty, and long-term oncologic risk. While emerging acellular options like exosomes and EVs may mitigate these concerns, their mechanisms of action, dosing strategies, and persistence *in vivo* need a clearer definition. Moreover, global standardization of potency assays will be essential for regulatory progression[20,31].

Personalized and AI-Driven Reconstruction

Advances in imaging, 3D bioprinting, and AI-enabled design suggest a future in which breast reconstruction is personalized to each patient's anatomy, biology, and treatment history. However, the integration of patient-specific immune profiles, radiation exposure, and tissue quality into scaffold or graft selection remains underexplored[34].

Cross-Disciplinary Integration

Perhaps the greatest opportunity and challenge lies in bridging traditionally siloed disciplines such as oncology, biomaterials, computational biology, and surgery. Effective translation will require not only

technological innovation but also crosstalk between immune modulation and regenerative design.

CONCLUSIONS

The integration of regenerative medicine with immunotherapy represents a paradigm shift in breast cancer management. NK cell-based therapies, MSC applications, and biomaterial scaffolds are no longer isolated innovations but are increasingly interconnected strategies shaping next-generation treatment. Advances in tissue engineering have enabled the development of scaffold systems that support not only structural regeneration but also immunomodulation, opening new possibilities for post-mastectomy reconstruction. Meanwhile, AI and multi-omics profiling are enhancing precision in patient stratification, therapy design, and clinical decision-making. Despite these promising developments, translational challenges remain, particularly those related to patient heterogeneity, standardization of cell-based products, regulatory complexity, and cost-effectiveness. Future clinical progress will depend on collaborative efforts that bridge basic science, engineering, and clinical oncology. By aligning biological insights with biomaterial innovations and computational tools, the field is moving closer to truly personalized, durable, and immune-integrated care for breast cancer patients.

ABBREVIATIONS

ADM (Acellular Dermal Matrix), **ADSCs** (Adipose-Derived Stem Cells), **AI** (Artificial Intelligence), **ALT-803** (IL-15 Superagonist), **CAR** (Chimeric Antigen Receptor), **CAR-NK** (Chimeric Antigen Receptor Natural Killer), **CAR-T** (Chimeric Antigen Receptor T), **CD** (Cytosine Deaminase), **CRISPR/Cas9** (Clustered Regularly Interspaced Short Palindromic Repeats / CRISPR-associated Protein 9), **dECM** (Decellularized Extracellular Matrix), **DIEP** (Deep Inferior Epigastric Perforator flap), **EVs** (Extracellular Vesicles), **GelMA** (Gelatin Methacryloyl), **GMP** (Good Manufacturing Practice), **GVHD** (Graft-Versus-Host Disease), **HER2** (Human Epidermal Growth Factor Receptor 2), **HLA** (Human Leukocyte Antigen), **IDO** (Indoleamine 2,3-dioxygenase), **iCasp9** (Inducible Caspase-9), **IL-2, IL-10, IL-15, IL-18, IL-21** (Interleukins), **LMICs** (Low- and Middle-Income Countries), **MICA/B** (MHC Class I Polypeptide-Related Sequence A/B), **MSCs** (Mesenchymal Stem Cells), **MUC1** (Mucin 1), **NK** (Natural Killer cell), **PEG** (Polyethylene Glycol), **PLGA** (Poly(lactic-co-glycolic acid)), **PGE2** (Prostaglandin E2), **SVM** (Support Vector Machine), **TGF-β** (Transforming Growth Factor Beta), **TME** (Tumor Microenvironment), **TNBC** (Triple-Negative Breast Cancer), **TRAM** (Transverse Rectus Abdominis Myocutaneous flap)

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AUTHOR'S CONTRIBUTIONS

Nur Shuhaidatul Sarmiza Abdul Halim and Monai Wisasi contributed equally to this work and were responsible for the primary writing and preparation of the manuscript. Ruttachuk Rungsisiwut, Rafeezul Mohamed, and Bakiah Shaharuddin contributed to the critical revision and refinement of the manuscript. Natthima Suwan and Nur Fitriyani Afiqah Abu Bakar assisted with the literature review and analysis of the relevant research. Mohammad Ghozali and Nur Atik provided additional support in reviewing the sources and ensuring the manuscript's coherence. Mas Rizky AA Syamsunarno assisted with the conceptual framework for the review. Aungkura Supokawej and Badrul Hisham Yahaya supervised the overall project and are the corresponding authors of this work. All authors read and approved the final manuscript.

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AVAILABILITY OF DATA AND MATERIALS

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

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CONSENT FOR PUBLICATION

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DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work, the authors used OpenAI's ChatGPT to assist with language editing, structure refinement, and formatting. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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