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Review

Bioengineered tracheal graft with enhanced vascularization and mechanical stability for functional airway reconstruction

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ABSTRACT

Tracheal reconstruction remains a formidable clinical challenge due to the complex structural, biomechanical, and physiological requirements of the airway. Traditional approaches, including autologous grafts, allografts, and synthetic prostheses, suffer from limitations such as donor site morbidity, immune rejection, and mechanical instability. Tissue-engineered tracheal grafts have emerged as a promising alternative, integrating advanced biomaterials, cellular therapies, and biofabrication techniques to create functional airway replacements. Synthetic polymers, such as polycaprolactone and polylactic acid, provide mechanical stability and tunable degradation properties, while extracellular matrix - derived biomaterials enhance biocompatibility and support cellular integration. Recent advances in stem cell biology, particularly the application of mesenchymal stem cells, induced pluripotent stem cells, and adipose-derived stem cells, have facilitated cartilage regeneration, epithelialization, and immune modulation within engineered constructs. However, achieving adequate vascularization remains a major bottleneck, necessitating the development of pre-vascularized scaffolds, growth factor delivery systems, and in vivo bioreactor strategies. Emerging technologies, including 3D bioprinting, electrospinning, and AI-driven scaffold design, are transforming the landscape of tracheal tissue engineering by enabling precise control over scaffold architecture, cellular distribution, and functional integration. Despite these advances, challenges such as mechanical failure, chronic inflammation, and regulatory hurdles must be addressed to ensure clinical translation. This review critically examines the latest advancements, persisting challenges, and future perspectives in artificial trachea engineering, providing a comprehensive roadmap for its development and clinical implementation.

Contents

Abbreviations: TET, Tissue-engineered Trachea; MSCs, Mesenchymal Stem Cells; iPSCs, Induced Pluripotent Stem Cells; VEGF, Vascular Endothelial Growth Factor; TGF-β, Transforming Growth Factor-beta; PCL, Polycaprolactone; PLA, Polylactic Acid; PLGA, Poly(lactic-co-glycolic acid); PEG, Polyethylene Glycol; ECM, Extracellular Matrix; BMSCs, Bone Mmarrow-derived Mesenchymal Stem Cells; ADSCs, Adipose-derived Stem Cells; TGF-β1, Transforming Growth Factor-beta 1; GAGs, Glycosaminoglycans; IL-10, Interleukin-10; HGF, Hepatocyte Growth Factor; PGE2, Prostaglandin E2; miRNAs, MicroRNAs; EGF, Epidermal Growth Factor; ALI, Air-liquid Interface; MUC5AC, Mucin 5AC; bFGF, Fibroblast Growth Factor; AVL, Arteriovenous Loop; PEEK, Polyetheretherketone; PU, Polyurethane; FEA, Finite Element Analysis; Tregs, Regulatory T cells; MHC, Major Histocompatibility Complex; GMP, Good Manufacturing Practice; AI, Artificial Intelligence; CT, Computed Tomography; MRI, Magnetic Resonance Imaging; GANs, Generative Adversarial Networks.

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1. Introduction

The trachea serves as a vital conduit for airflow, playing a pivotal role in respiratory physiology by maintaining airway patency and facilitating gas exchange. Structural defects of the trachea, whether congenital or acquired, pose severe and often life-threatening risks, necessitating prompt and effective intervention. These defects arise from a spectrum of etiologies, including congenital anomalies such

as tracheomalacia and complete tracheal rings, traumatic injuries resulting from blunt or penetrating forces, prolonged intubation leading to post-intubation tracheal stenosis, and malignant neoplasms either originating in the trachea or invading from adjacent structures. Notably, the incidence of tracheal stenosis has increased in recent years due to the widespread use of prolonged mechanical ventilation, highlighting an urgent clinical need for advanced reconstructive strategies. Despite significant progress in surgical techniques, achieving a durable and functional tracheal replacement remains an ongoing challenge [1,2].

Current tracheal reconstruction strategies primarily rely on autologous grafts, allografts, and synthetic prostheses, each of which presents distinct limitation (Fig. 1) [2]. Autologous grafts, commonly harvested from costal cartilage or auricular cartilage, provide inherent biocompatibility but suffer from donor site morbidity, limited availability, and mechanical insufficiency. Allografts, including decellularized tracheal matrices, offer structural support but are frequently compromised by immune rejection, incomplete integration, and long-term degradation. Synthetic prostheses, such as silicone stents and metallic implants, can restore airway continuity but are plagued by complications including migration, infection, biofilm formation, and restenosis (Fig. 2). These limitations underscore the necessity for innovative solutions capable of mimicking the biomechanical, structural, and physiological properties of the native tracheas [3].

The advent of tissue engineering has revolutionized the landscape of tracheal reconstruction, offering a regenerative approach that combines biomaterials, cellular components, and bioactive factors to restore native-like function. A successful tissue-engineered trachea (**TET**) must fulfill several fundamental criteria: biocompatibility to prevent immune rejection, sufficient mechanical strength to withstand respiratory forces, epithelialization to restore mucociliary clearance, and vascularization to ensure graft survival and integration. Advances in biomaterials science have facilitated the development of biopolymeric scaffolds, hybrid composites, and bioactive matrices that support cell adhesion, proliferation, and differentiation. Moreover, cutting-edge biofabrication techniques, such as 3D bioprinting, enable the precise spatial deposition of cells and biomaterials, paving the way for patient-specific, anatomically accurate constructs [4].

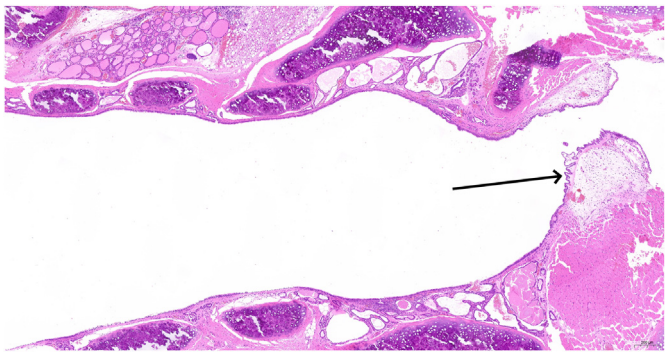

Fig. 2. Histological Image of Tracheal Restenosis. Note: Histological section showing restenosis at the site of a synthetic tracheal prosthesis. The arrow indicates the presence of excessive fibroproliferative tissue, leading to airway narrowing. Restenosis is a common complication of synthetic implants, often resulting from chronic inflammation and tissue overgrowth.

In parallel, cellular therapies have emerged as a cornerstone of regenerative tracheal engineering. Stem cell-based approaches, particularly utilizing mesenchymal stem cells (**MSCs**) and induced pluripotent stem cells (**iPSCs**), have demonstrated immense potential in promoting cartilage regeneration, epithelialization, and immunomodulation. Additionally, the strategic delivery of growth factors, including vascular endothelial growth factor (**VEGF**) and

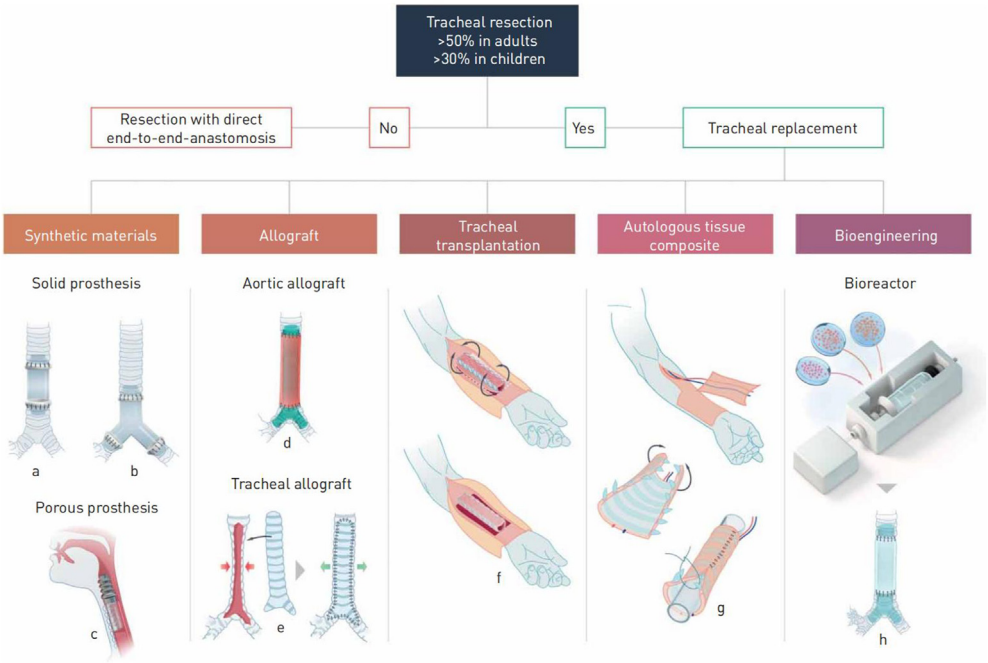

Fig. 1. Strategies for Tracheal Replacement and Reconstruction. Note: Different approaches for tracheal replacement when direct end-to-end anastomosis is not feasible. These include synthetic prostheses, allografts, tracheal transplantation, autologous tissue grafts, and bioengineered constructs using bioreactors. Bioengineering offers a promising alternative by integrating stem cells and biomaterials to create functional airway grafts.

transforming growth factor-beta (**TGF-β**), has been explored to enhance neovascularization and accelerate tissue integration. Despite these promising developments, several critical challenges persist, including ensuring long-term graft viability, optimizing host integration, and establishing reproducible, clinically translatable methodologies [4,5]. The integration of multidisciplinary advances in biomaterials, cellular engineering, and biofabrication heralds a new era in tracheal reconstruction, with the potential to achieve fully functional, patient-specific bioengineered tracheas. However, significant hurdles remain in terms of scalability, regulatory approval, and long-term clinical outcomes. Addressing these challenges requires continued research, interdisciplinary collaboration, and rigorous preclinical and clinical validation to translate laboratory innovations into viable clinical therapies [5].

2. Structural, functional, and biomechanical foundations of trachea

2.1. Architectural and cellular composition of the native trachea

The trachea is a specialized, semi-rigid tubular structure composed of a series of C-shaped hyaline cartilage rings that provide mechanical stability while maintaining the flexibility required for respiration. The posterior tracheal wall, consisting of smooth muscle and fibrous connective tissue, allows dynamic modulation of airway diameter in response to physiological demands. The luminal surface is lined by pseudostratified ciliated columnar epithelium, playing a critical role in mucociliary clearance and innate immunity by preventing the accumulation of pathogens and particulates. Additionally, submucosal glands contribute to airway hydration through mucus secretion, further enhancing airway defense mechanisms [6].

2.2. Vascularization and microcirculatory challenges in tracheal reconstruction

The trachea is perfused by segmental branches of the inferior thyroid, bronchial, and internal thoracic arteries, forming an intricate microvascular network that ensures oxygen and nutrient delivery. This vascularization is essential for maintaining cellular viability and promoting tissue repair. However, reconstructing a fully vascularized artificial trachea remains a major challenge. Insufficient microcirculatory development often leads to ischemia, delayed healing, and graft failure. Recent advances in vascular tissue engineering have explored pre-vascularized scaffolds, controlled angiogenic factor release, and in vivo bioreactor techniques to address this limitation, with promising experimental outcomes [7,8].

2.3. Biomechanical criteria for an optimal artificial trachea

A fully functional artificial trachea must withstand constant respiratory forces while preserving airway patency. Key mechanical properties include radial stiffness to prevent collapse, longitudinal flexibility to adapt to cervical and thoracic movements, and sufficient compressive strength to resist intrathoracic pressure fluctuations. Additionally, engineered constructs must minimize anastomotic stress, as excessive tension can cause dehiscence or post-surgical stenosis. Advanced bioresorbable polymer composites and dynamic scaffolds incorporating elastomeric components are being investigated to optimize these biomechanical properties, ensuring long-term functional stability [9].

2.4. Translational relevance of preclinical models for tracheal engineering

Preclinical models play a crucial role in evaluating the structural, functional, and immunological compatibility of engineered tracheal constructs. Large animal models such as pigs closely mirror human tracheal anatomy and biomechanics, making them particularly valuable for translational studies. Smaller models, including rabbits and ferrets, offer cost-effective alternatives for early-stage assessments of cell integration and immune response. Recent studies have also employed computational modeling and in vitro bioreactors to simulate in vivo conditions, refining scaffold designs before in vivo implantation. These advancements are accelerating the development of clinically viable bioengineered tracheal grafts.

A comprehensive understanding of the trachea's architecture, vascularization, and biomechanical properties is fundamental to developing next-generation artificial tracheas. Addressing the challenges of vascular integration, mechanical resilience, and translational validation will be key to bridging the gap between experimental research and clinical application. As biofabrication technologies and regenerative medicine continue to evolve, the prospect of fully functional, bioengineered tracheal replacements is steadily approaching clinical reality [10].

3. Biomaterials for artificial trachea engineering

3.1. Synthetic polymer-based scaffolds

Synthetic polymers have been extensively explored for artificial trachea engineering due to their tunable mechanical properties, processability, and ability to support cellular adhesion and proliferation. Among these, polycaprolactone (**PCL**), polylactic acid (**PLA**), and polyurethane (**PU**) have gained significant attention (Table 1) [11–30]. PCL is a biodegradable polymer with excellent mechanical stability and slow degradation kinetics, making it suitable for load-bearing applications such as tracheal scaffolds. However, its hydrophobic nature limits cellular infiltration and integration. PLA, a widely used bioresorbable polymer, offers good biocompatibility and tunable mechanical properties but is brittle compared to PCL, requiring composite reinforcement. PU, known for its elasticity and resilience, has been investigated for dynamic airway applications due to its ability to withstand repetitive mechanical stress [11,17,19].

Poly(lactic-co-glycolic acid) (**PLGA**) and polyethylene glycol (**PEG**) are also frequently employed in artificial trachea engineering. PLGA is a copolymer with adjustable degradation rates based on the lactic-to-glycolic acid ratio, allowing for controlled scaffold resorption. Its use in tracheal reconstruction has been enhanced through blending with bioactive molecules to promote tissue integration. PEG, a hydrophilic polymer, is primarily utilized to modify surface properties and enhance biocompatibility. Despite their advantages, these synthetic polymers often lack intrinsic bioactivity and require functionalization with extracellular matrix (**ECM**) components, peptides, or growth factors to improve cell adhesion and differentiation [20,22].

The advent of 3D printing has revolutionized the design and fabrication of patient-specific tracheal implants using these synthetic polymers. 3D-printed scaffolds offer precise control over pore geometry, interconnectivity, and mechanical properties, facilitating customized airway replacements. Studies have demonstrated the feasibility of incorporating cell-laden hydrogels and bioinks into polymeric frameworks, allowing for concurrent bioprinting of

Table 1
Comparison of synthetic and natural biomaterials.

Material	Strength	Degradation	Cell Support	Immunogenicity	Porosity	Vascularization	Fabrication	Benefits	Limitations
PCL [11–13]	High	Slow (>2 years)	Moderate	Low	Moderate	Low	3D printing, electrospinning	Excellent mechanical properties, tunable porosity, well-suited for 3D printing	Slow degradation may lead to prolonged foreign body reaction, low intrinsic bioactivity
PLA [14,15]	Moderate	Medium (6–24 months)	Good	Low to moderate	Moderate	Low to moderate	3D printing, injection molding	Biodegradable, moderate mechanical properties, suitable for load-bearing applications	Degradation products may induce local inflammation, requires surface modifications for improved bioactivity
PLGA [16,17]	Low to moderate	Adjustable (weeks to months)	Good	Low to moderate	Moderate to high	Moderate	Electrospinning, scaffold casting	Tunable degradation rates, widely used in tissue engineering	Degradation byproducts (lactic/glycolic acid) can lower local pH, leading to inflammation
PU [18,19]	High	Non-degradable or very slow	Good	Low	Moderate	Low	Electrospinning, solvent casting	Excellent mechanical stability, high elasticity, suitable for dynamic airway environments	Long-term implantation may cause chronic inflammation, requires biocompatible modifications
PEG [20,21]	Low	Fast (days to weeks)	Excellent	Low	High	High	Hydrogel-based 3D printing, injectable scaffolds	High hydrophilicity, supports cell adhesion and bioactive factor delivery	Poor mechanical strength, requires reinforcement for structural integrity
Natural ECM [22,23]	Low to moderate	Fast (weeks to months)	Excellent	Low	High	High	Decellularization, hydrogel casting	Retains native ECM proteins, supports cell attachment and tissue remodeling	Source-dependent variations, potential for residual immunogenicity
Collagen-Based Scaffolds [24,25]	Low	Fast (weeks)	Excellent	Low	High	High	Electrospinning, hydrogel scaffolds	Supports cell proliferation and differentiation, biodegradable	Poor mechanical strength, rapid degradation
Gelatin-Based Hydrogels [26,27]	Low	Fast (days to weeks)	Excellent	Low	High	High	Hydrogel casting, bioprinting	Good biocompatibility, tunable degradation	Poor mechanical properties, requires reinforcement
Hybrid materials (e.g., PCL-ECM, PLA-HA, PU-collagen) [28–30]	Adjustable	Adjustable	Excellent	Low to moderate	High	High	3D bioprinting, composite scaffolds	Combines structural stability with bioactivity, promotes cell integration	Complex fabrication, potential challenges in batch-to-batch consistency

structural and cellular components. Additionally, recent advances in multi-material printing have enabled the fabrication of gradient scaffolds that mimic the heterogeneity of the native trachea, improving both mechanical and biological integration [3,5].

Despite these advancements, challenges remain in optimizing scaffold degradation rates, ensuring long-term mechanical stability, and achieving functional vascularization. Future research is focused on developing bioactive synthetic polymers that can dynamically respond to the host environment, incorporating stimuli-responsive materials and smart drug delivery systems to enhance regeneration and reduce post-implantation complications.

3.2. Natural biomaterials and hybrid approaches

3.2.1. Decellularized tracheal matrices: ECM preservation vs. mechanical compromise

Decellularized tracheal matrices have been widely investigated as scaffolds for airway reconstruction due to their ability to retain native ECM components while providing an immunologically inert framework for cellular repopulation. Various decellularization protocols, including enzymatic, chemical, and physical treatments, have been explored to remove cellular components while preserving ECM integrity. However, an inherent challenge is the trade-off between effective cellular removal and the retention of biomechanical properties. Overly aggressive decellularization can lead to structural weakening, while insufficient processing may leave residual immunogenic material, triggering host immune responses. To enhance their mechanical performance, decellularized scaffolds are often crosslinked using chemical agents or reinforced with synthetic polymeric materials, allowing for improved durability and long-term implantation outcomes [31–34].

3.2.2. Hydrogels as bioinks for 3D bioprinting

Hydrogels, composed of naturally derived biomolecules such as collagen, hyaluronic acid, alginate, and fibrin, have gained traction in artificial trachea engineering as bioinks for 3D bioprinting. Their high water content provides a supportive microenvironment for cellular proliferation and differentiation, closely mimicking the native extracellular niche. Advances in biofabrication have enabled the encapsulation of growth factors and stem cells within hydrogel matrices, promoting site-specific tissue regeneration. Recent studies have demonstrated that dynamic hydrogel formulations with tunable stiffness can modulate cellular behaviors, guiding epithelialization and chondrogenesis to reconstruct functional airway tissues [35–38].

3.2.3. Hybrid biomaterials for enhanced integration and mechanical stability

Hybrid biomaterials integrating both natural and synthetic components have shown promise in enhancing mechanical resilience and biological integration. These composites leverage the bioactivity of natural ECM proteins while benefiting from the structural integrity of synthetic polymers. Strategies such as electrospinning, layer-by-layer assembly, and nanocomposite reinforcement have been employed to develop hybrid scaffolds with improved mechanical strength, biodegradability, and cellular compatibility, bringing engineered tracheal replacements closer to clinical application [18,39–41].

3.3. Scaffold-free tracheal engineering strategies

3.3.1. Cartilage-epithelium sheet-based biofabrication

Scaffold-free tracheal engineering represents an emerging paradigm in regenerative medicine, focusing on the self-assembly and functional maturation of cellular constructs without the use of exogenous biomaterial scaffolds. This strategy aims to overcome the limitations associated with synthetic and natural biomaterial-based scaffolds, such as immune rejection, long-term biodegradation concerns, and biomechanical mismatches with native tracheal tissue [42,43].

One promising approach is cartilage-epithelium sheet-based biofabrication, which utilizes layered cell sheets composed of autologous chondrocytes and epithelial cells. These sheets, expanded ex vivo, are stacked in a controlled manner to replicate the histological organization of the native trachea. Preconditioning these constructs in dynamic bioreactors has been shown to enhance ECM deposition, improve mechanical properties, and facilitate graft integration post-implantation. Recent studies have demonstrated that chondrocyte-derived ECM can provide essential biochemical and structural cues for epithelialization, leading to superior functional outcomes [44].

3.3.2. Autologous scaffold-free approaches without synthetic supports

Autologous scaffold-free approaches without synthetic supports leverage cell sheet engineering and self-assembling tissue spheroids to generate structurally stable tracheal constructs. By utilizing patient-derived cells, these constructs minimize immunogenic risks and promote seamless host integration. However, one of the primary challenges of this approach is achieving sufficient biomechanical strength to withstand respiratory pressures while maintaining long-term functionality. Emerging solutions include the use of conditioned media enriched with growth factors and mechanical stimulation protocols to enhance tissue robustness and extracellular matrix organization [45–47].

3.3.3. Silk fibroin-polycaprolactone composites for biomimetic designs

PCL composites for biomimetic designs represent a hybrid strategy that merges scaffold-free and biomaterial-assisted techniques. Silk fibroin, known for its biocompatibility and mechanical resilience, has been integrated with PCL through electrospinning and 3D printing to create highly organized fibrous networks that mimic the extracellular architecture of native tracheal tissue. This approach has shown promise in enhancing cellular adhesion, ECM deposition, and tissue remodeling, making it a viable alternative to conventional scaffold-based tracheal replacements [18,48,49].

3.4. Advanced fabrication techniques

Advancements in fabrication techniques have significantly enhanced the development of artificial tracheal scaffolds, improving their structural fidelity, cellular compatibility, and biomechanical performance. The integration of cutting-edge technologies, such as 3D bioprinting, electrospinning, freeze-drying, salt-leaching, and layered assembly, has enabled the precise control of scaffold architecture and composition, optimizing cellular attachment, nutrient diffusion, and long-term functional integration [50,51].

3.4.1. 3D bioprinting: multimaterial and cell-laden constructs

3D bioprinting has emerged as a transformative technology in artificial trachea engineering, allowing for the precise deposition of biomaterials and living cells in a spatially controlled manner. Unlike conventional scaffold fabrication techniques, 3D bioprinting enables the generation of patient-specific constructs with tunable biomechanical properties and intricate microarchitectures that closely mimic the native trachea. Current strategies incorporate a combination of synthetic polymers (e.g., PCL, PLGA) and natural bioinks (e.g., collagen, fibrin, hyaluronic acid) to enhance cellular

integration. Furthermore, advances in multimaterial printing allow for the fabrication of heterogeneous constructs in which mechanically robust cartilage-like regions are interwoven with epithelial-supportive matrices, fostering the development of functional airway tissue. Recent studies have demonstrated that the co-printing of mesenchymal stem cells and chondrocytes within hydrogel-laden scaffolds promotes cartilage differentiation and long-term mechanical stability, paving the way for clinically viable bioengineered tracheas [50].

3.4.2. Electrospinning, freeze-drying, and salt-leaching for optimized porosity

Porosity is a critical parameter in tracheal scaffold design, influencing cellular infiltration, vascularization, and mechanical performance. Electrospinning, freeze-drying, and salt-leaching techniques have been widely applied to optimize scaffold porosity at both micro- and nanoscale levels. Electrospinning facilitates the fabrication of ultrafine fibrous matrices resembling the native extracellular matrix, promoting epithelial cell adhesion and proliferation. Recent innovations in electrospinning technology have introduced co-electrospun composites integrating biodegradable polymers with bioactive molecules, enhancing tracheal tissue regeneration. Freeze-drying, on the other hand, produces highly porous structures with interconnected channels, improving nutrient diffusion and waste removal in engineered constructs. This technique is particularly useful in the development of cartilage-like tracheal segments, where adequate chondrocyte infiltration is required for long-term functional stability. Salt-leaching, a simple yet effective porogen-based method, has been employed to generate tunable pore architectures in polymeric scaffolds, optimizing mechanical resilience while maintaining adequate cellular accessibility [3,11,50].

3.4.3. Layered assembly techniques for composite scaffolds

The structural complexity of the trachea necessitates the development of multi-layered composite scaffolds that can replicate its hierarchical organization. Layered assembly techniques enable the fabrication of scaffolds that incorporate distinct functional regions, including an inner epithelial-supportive layer, a middle load-bearing cartilage-like region, and an outer vascular-integrative matrix. Advances in biofabrication have demonstrated that sequential deposition of cell-laden hydrogels, electrospun fibers, and mechanically reinforced composites can significantly improve the structural and biological integration of engineered tracheal grafts. Hybrid approaches, such as layer-by-layer assembly combined with 3D bioprinting, have further enhanced scaffold performance by providing tunable stiffness gradients and site-specific bioactivity. These innovations hold promise for the development of fully functional tracheal replacements with improved long-term clinical outcomes [19,51].

4. Cellular strategies for tracheal tissue engineering

4.1. Stem cell applications in tracheal engineering

Stem cell-based approaches have gained significant traction in tracheal tissue engineering due to their multilineage differentiation potential, immunomodulatory properties, and capacity to enhance vascularization. The ability of stem cells to differentiate into chondrocytes, epithelial cells, and supportive stromal components is crucial for developing functional tracheal replacements. Several stem cell sources have been extensively studied, including bone marrow-derived mesenchymal stem cells (**BMSCs**), iPSCs, and adipose-derived stem cells (**ADSCs**), each offering distinct advantages and challenges in tracheal regeneration (Table 2) [52–61].

Table 2
Comparison of different stem cell sources for tracheal engineering.

Cell Type	Differentiation Potential	Immune Modulation	2Ease of Harvesting	Proliferation Rate	Clinical Applications	Challenges
BMSCs [52–55]	High (cartilage, bone, epithelium)	Strong (secretes anti-inflammatory cytokines, reduces fibrosis)	Moderate (requires bone marrow aspiration, invasive)	Moderate (limited by donor age and culture conditions)	Widely studied for tracheal cartilage regeneration and immunomodulation	Donor variability, invasive harvesting, aging-related decline in potency
iPSCs [56–58]	Very high (can differentiate into all three germ layers)	Variable (depends on differentiation stage, potential immunogenicity if incompletely reprogrammed)	Low (requires genetic reprogramming, labor-intensive)	High (unlimited proliferation capacity in undifferentiated state)	Promising for patient-specific tissue engineering, but safety concerns remain	Risk of tumorigenesis, long differentiation protocols, complex regulatory hurdles
ADSCs [59–61]	Moderate (mainly cartilage, fibroblasts, epithelium)	Strong (anti-inflammatory, promotes tissue remodeling)	High (minimally invasive liposuction, abundant source)	High (expands efficiently in culture)	Potential for epithelial repair, cartilage support, and immune regulation	Variability in differentiation efficiency, requires optimization for airway applications

4.1.1. BMSCs for cartilage regeneration

BMSCs are one of the most widely investigated stem cell sources in tracheal tissue engineering due to their accessibility, chondrogenic potential, and immunomodulatory effects. These cells have demonstrated the ability to differentiate into chondrocytes when cultured in three-dimensional environments supplemented with chondrogenic factors such as transforming growth factor-beta (**TGF-β1**), bone morphogenetic proteins (BMP-2 and BMP-7), and dexamethasone. Preclinical studies have shown that BMSC-seeded scaffolds promote the deposition of type II collagen and glycosaminoglycans (**GAGs**), both of which are critical for the mechanical integrity and resilience of engineered tracheal cartilage [52,53].

Despite their promising regenerative properties, several challenges must be addressed to optimize BMSC-based therapies. Donor age and passage number influence BMSC proliferation and differentiation capacity, necessitating stringent selection criteria. Additionally, ensuring homogeneous differentiation across the entire scaffold remains difficult, as oxygen and nutrient gradients within large constructs can lead to incomplete cartilage maturation. To overcome these limitations, dynamic bioreactors and hypoxia preconditioning have been employed to enhance chondrogenesis and ECM production, improving long-term graft viability [54,55].

4.1.2. iPSCs for epithelium and cartilage differentiation

iPSCs represent a groundbreaking advancement in regenerative medicine, offering an unlimited source of patient-specific cells that can differentiate into multiple tracheal lineages. Directed differentiation protocols have enabled the generation of functional airway epithelial cells and chondrocytes from iPSCs, mimicking the structural and functional complexity of the native trachea. Recent studies have demonstrated that iPSC-derived chondrocytes exhibit superior ECM deposition and mechanical properties compared to primary chondrocytes, making them highly suitable for tracheal cartilage reconstruction [56].

However, the clinical translation of iPSCs remains challenging due to concerns regarding genomic instability, differentiation efficiency, and the risk of tumorigenesis. Strategies such as small molecule-based lineage specification, genetic editing using CRISPR-Cas9, and the incorporation of biomimetic cues within 3D scaffolds are being explored to enhance the safety and efficacy of iPSC-derived tracheal constructs. Moreover, bioprinting technologies have enabled the fabrication of spatially controlled iPSC-derived constructs, allowing for precise integration of epithelial and cartilage compartments within engineered tracheal grafts [57,58].

4.1.3. ADSCs for immune modulation and tissue remodeling

ADSCs have emerged as an attractive cell source for tracheal tissue engineering due to their ease of isolation, high proliferative capacity, and immunoregulatory effects. These cells secrete a variety of bioactive factors, including interleukin-10 (IL-10), hepatocyte growth factor (**HGF**), and prostaglandin E2 (**PGE2**), which modulate immune responses, reduce inflammation, and promote tissue remodeling. In addition to their immunomodulatory functions, ADSCs possess chondrogenic and epithelial differentiation potential, making them ideal candidates for composite tracheal grafts [59,60].

Despite their advantages, ADSC-based therapies require further optimization in terms of differentiation consistency and long-term functionality. The incorporation of extracellular matrix-derived hydrogels and biochemical conditioning strategies has been shown to enhance ADSC-mediated cartilage and epithelium regeneration, improving tracheal graft integration and durability (Fig. 3) [61].

4.2. Epithelialization and airway protection

Efficient epithelialization is critical for the success of engineered tracheal grafts, as it provides a protective mucosal barrier, facilitates mucociliary clearance, and prevents bacterial colonization. A fully functional epithelium minimizes granulation tissue formation and fibrosis, ensuring long-term graft patency. Several advanced strategies have been developed to promote epithelialization and enhance airway protection, including exosome-mediated epithelial regeneration, pre-epithelialized grafts, and alternative epithelial cell sources such as skin-derived epithelial cells [62].

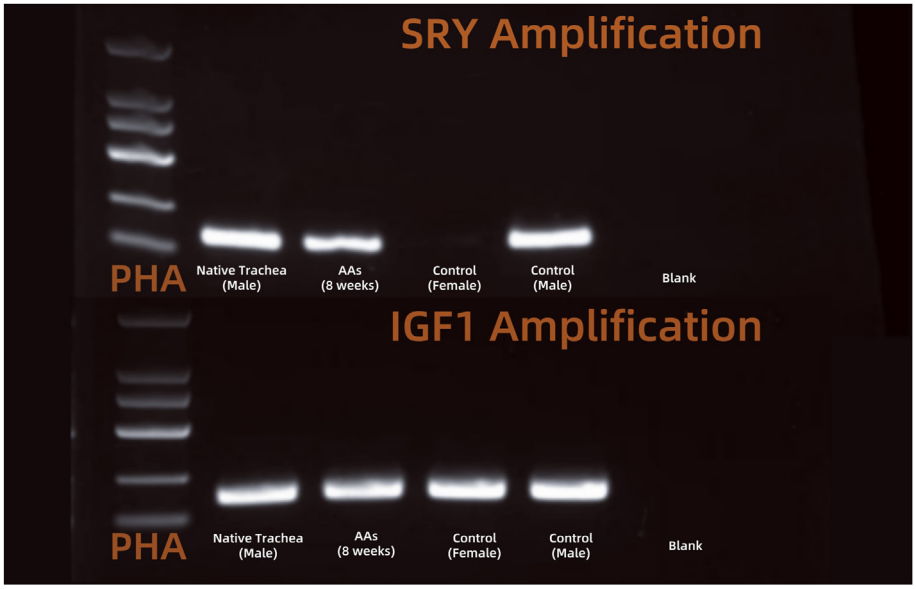

Fig. 3. PCR Confirmation of Recipient-Derived Tissue in Engineered Trachea. Note: Polymerase chain reaction (PCR) analysis showing SRY gene amplification (a male-specific marker) and IGF1 gene amplification in native tracheal tissue, allogeneic airway segments (AAs) at 8 weeks, and control samples. The absence of SRY amplification in female controls and its presence in male-derived tissues confirm that regenerated tracheal structures originate from the recipient rather than the donor.

4.2.1. Exosome-mediated strategies for rapid epithelial regeneration

Exosomes, extracellular vesicles secreted by various cell types, play a crucial role in intercellular communication by transferring bioactive molecules such as microRNAs (**miRNAs**), proteins, and lipids. Recent studies have demonstrated that exosomes derived from MSCs and epithelial progenitor cells can enhance epithelial regeneration by promoting cell proliferation, migration, and differentiation. Specifically, exosomal miRNAs such as miR-21 and miR-146a have been shown to modulate inflammatory responses and accelerate epithelial repair [63].

Preclinical studies indicate that applying exosome-enriched hydrogels to tracheal scaffolds significantly enhances epithelial coverage and reduces the risk of fibrosis. Moreover, engineered exosomes loaded with specific growth factors, including epidermal growth factor (**EGF**) and HGF, have been explored to further accelerate epithelial regeneration. The integration of exosome-based therapies with advanced scaffold designs offers a promising approach to achieving a fully functional airway lining [64,65].

4.2.2. Pre-epithelialized grafts: minimizing fibrosis and inflammatory responses

Pre-epithelialization of tracheal grafts prior to implantation has emerged as a promising strategy to mitigate early inflammatory responses and prevent fibrosis. By pre-seeding engineered constructs with autologous epithelial cells, researchers aim to create a confluent epithelial layer capable of resisting environmental challenges and microbial invasion. Various culture techniques, including air-liquid interface (**ALI**) systems, have been employed to enhance epithelial cell differentiation and functional maturation in vitro before graft transplantation [66].

Clinical studies suggest that pre-epithelialized grafts exhibit reduced postoperative complications, including stenosis and excessive fibrotic remodeling. Furthermore, co-culturing epithelial cells with fibroblasts and endothelial cells in dynamic bioreactors has been shown to improve epithelial barrier function and enhance long-term graft integration. Despite these advances, challenges such as maintaining epithelial viability during graft storage and transportation remain to be addressed before widespread clinical adoption [67].

4.2.3. Skin-derived epithelial cells for alternative airway linings

The use of skin-derived epithelial cells has been investigated as an alternative strategy for tracheal reconstruction, particularly in cases where respiratory epithelial cell sourcing is limited. Keratinocytes, the predominant cell type in the epidermis, share several functional characteristics with airway epithelial cells, including the ability to form a protective barrier. Recent studies have demonstrated that keratinocytes can be induced to express airway-specific markers such as mucin 5AC (**MUC5AC**) and forkhead box protein J1 (**FOXJ1**) when cultured under appropriate differentiation conditions [68,69].

4.3. Vascularization and angiogenesis strategies

Vascularization is a critical factor in the success of engineered tracheal grafts, as adequate blood supply is essential for cell survival, nutrient diffusion, and long-term tissue integration. The trachea is a highly vascularized organ, receiving segmental blood supply from branches of the inferior thyroid, bronchial, and internal thoracic arteries. Failure to establish functional microvascular networks within bioengineered constructs often results in ischemia, fibrosis, and graft necrosis. To address these challenges, various approaches have been developed to promote vascular integration, including pre-vascularized grafts, growth factor delivery systems, and in vivo bioreactor techniques (Table 3) [36,70–74].

4.3.1. Pre-vascularized grafts with endothelial cell integration

Pre-vascularization strategies involve the incorporation of endothelial cells into engineered tracheal constructs to facilitate early capillary network formation upon implantation. EPCs and MSCs co-cultured within decellularized scaffolds or biopolymer matrices have demonstrated enhanced neovascularization in preclinical models. By pre-seeding these constructs with endothelial cells in vitro, researchers have successfully induced capillary-like structures, which anastomose with host vasculature post-implantation, improving graft perfusion and reducing hypoxic damage [36,70].

Advanced biofabrication techniques, including microfluidic bioprinting and vascularized organoids, have been explored to generate pre-formed vascular networks within engineered tracheal scaffolds. These approaches mimic the hierarchical architecture of native blood vessels, ensuring adequate oxygenation and metabolic exchange. Studies have shown that perfused pre-vascularized scaffolds significantly enhance epithelialization rates and chondrocyte survival, highlighting the potential of endothelial cell integration in improving graft longevity [36,70].

4.3.2. Growth factor delivery systems: VEGF, bFGF, TGF-β

Angiogenic growth factors play a pivotal role in stimulating vascularization within engineered tissues. Among these, VEGF is the most extensively studied due to its ability to induce endothelial cell proliferation, migration, and capillary sprouting. Sustained release of VEGF from biomaterial scaffolds has been shown to accelerate neovascularization and improve tissue integration. Additionally, fibroblast growth factor (**bFGF**) enhances angiogenesis by promoting fibroblast proliferation and extracellular matrix remodeling, while TGF-β modulates vascular stability and tissue regeneration [71].

Several delivery strategies have been investigated to optimize the localized and controlled release of angiogenic factors. Encapsulation of VEGF within biodegradable microspheres, hydrogels, or nanofiber scaffolds enables prolonged release, reducing the need

Table 3
Comparison of vascularization and angiogenesis strategies.

Strategy	Mechanism	Advantages	Challenges	Clinical Applications
VEGF delivery [36,70]	Enhances endothelial cell proliferation and migration via VEGF release	Stimulates rapid angiogenesis, easy to incorporate into scaffolds	Requires controlled release to prevent aberrant vessel growth	Used in bioengineered tracheal grafts to enhance perfusion
Pre-Vascularized Grafts [71,72]	Grafts pre-seeded with endothelial cells to establish early vascular networks	Improves early graft integration, reduces ischemic necrosis	Complex fabrication, potential immune rejection	Applied in tissue-engineered constructs for airway reconstruction
In Vivo Bioreactor Approach [73,74]	Implantation in a vascularized environment before final transplantation	Mimics natural vascular development, enhances long-term graft survival	Additional surgical procedures, longer preparation time	Tested in preclinical models for tracheal and organ transplantation

for repeated administration. Moreover, gene therapy approaches utilizing viral and non-viral vectors have been explored to induce endogenous VEGF expression within host tissues, further enhancing vascularization potential. However, precise dosing and spatiotemporal control of growth factor release remain major challenges, requiring further refinement to minimize adverse effects such as aberrant vessel formation [72].

4.3.3. In vivo bioreactor approaches for vascularized pre-conditioning

In vivo bioreactor techniques involve the implantation of engineered constructs into well-vascularized regions of the body before their final transplantation into the airway. This strategy leverages the host's native vasculature to pre-condition grafts, promoting microvascular network formation prior to orthotopic transplantation. For example, omentum and arteriovenous loop (**AVL**) models have been utilized as in vivo bioreactors, providing a rich vascular bed that enhances endothelialization and graft maturation [73,74].

Recent studies have demonstrated that pre-conditioning engineered tracheal grafts within an in vivo bioreactor significantly improves long-term viability and reduces ischemic complications. Dynamic perfusion bioreactors, which mimic physiological blood flow conditions, have also been employed in vitro to enhance endothelialization and vascular integration before transplantation. While promising, these approaches require further optimization to balance host immune responses and ensure scalable clinical applications [74].

5. Challenges and limitations in artificial trachea development

5.1. Vascularization and tissue integration

Despite significant advancements in tissue engineering, achieving effective vascularization remains one of the most formidable challenges in artificial trachea development. A robust and functional microvascular network is essential for long-term graft viability, ensuring adequate oxygen and nutrient diffusion while preventing hypoxia-induced tissue necrosis. The trachea's unique vascular architecture, characterized by segmental blood supply, complicates the integration of engineered grafts, necessitating innovative strategies to establish functional neovascularization [75].

5.1.1. Microvascular network development for long-term graft viability

The establishment of a microvascular network within bioengineered tracheal constructs is critical for sustaining cell survival and function post-implantation. Current approaches include the incorporation of EPCs, the use of angiogenic growth factors such as VEGF and bFGF, and the development of perfusable microvascular channels within scaffold matrices. Recent studies have demonstrated that pre-seeding tracheal constructs with a combination of EPCs and MSCs enhances early vascular ingrowth, reducing the risk of ischemic graft failure [36,75].

Another promising strategy involves the fabrication of microchannel networks within biomaterial scaffolds using advanced bioprinting techniques. These microchannels mimic native capillary structures, facilitating endothelial cell attachment and guiding neovessel formation. Computational fluid dynamics models have also been employed to optimize scaffold porosity and interconnectivity, improving vascular infiltration and oxygen diffusion efficiency. However, despite these advancements, ensuring uniform and stable microvascular network formation remains a major challenge that requires further refinement [36].

5.1.2. Heterotopic pre-vascularization strategies and host tissue integration

Heterotopic pre-vascularization, wherein engineered grafts are implanted into a well-vascularized tissue site prior to tracheal reconstruction, has emerged as an effective approach to promoting early vascular integration. This technique leverages the host's native vascular bed to stimulate endothelialization and microcapillary formation before transplantation into the airway. Common pre-vascularization sites include the omentum, the groin, and AVL models, which provide an enriched angiogenic environment for graft conditioning [76].

Recent studies have demonstrated that pre-vascularized grafts exhibit superior integration and reduced postoperative complications compared to non-preconditioned constructs. In particular, omental wrapping has been shown to significantly improve epithelialization and prevent airway collapse by ensuring consistent blood supply. However, challenges such as immune-mediated responses, donor-site morbidity, and prolonged preconditioning durations must be addressed to optimize this approach for clinical application [77].

5.2. Mechanical and structural failures

The mechanical integrity of artificial tracheal constructs is one of the most pressing challenges in tracheal tissue engineering. The native trachea must endure continuous biomechanical stresses, including compressive forces generated during respiration, tensile forces due to neck movements, and cyclic pressure changes from coughing and swallowing. Failure to replicate these biomechanical properties in engineered constructs leads to complications such as airway collapse, anastomotic stenosis, and premature degradation of resorbable scaffolds, limiting their long-term functionality [78].

Resorbable synthetic scaffolds, such as PCL, PLGA, and PLA, have been extensively explored for tracheal tissue engineering due to their controlled degradation properties and tunable mechanical characteristics. However, their progressive loss of structural integrity over time poses a significant risk. Studies have shown that the degradation kinetics of these materials often outpace the rate of native tissue remodeling, leading to a mismatch in mechanical support and increasing the risk of graft collapse. To address this, efforts have focused on developing composite scaffolds that integrate slow-degrading polymers with bioactive reinforcements such as hydroxyapatite, graphene oxide, and carbon nanotubes to enhance mechanical stability while maintaining bioactivity [79].

Tracheal collapse is a major concern in bioengineered grafts, particularly in long-segment replacements where the absence of native cartilage rings exacerbates airway instability. To counteract this, various reinforcement strategies have been investigated. The incorporation of high-strength polymers, such as polyetheretherketone (**PEEK**) and polyurethane (**PU**), has been shown to significantly improve the mechanical resilience of engineered tracheal constructs. Additionally, computational modeling techniques, such as finite element analysis (**FEA**), have been utilized to optimize scaffold architectures, ensuring adequate load distribution and minimizing stress concentration zones.

Hybrid approaches that combine natural ECM-derived materials with synthetic reinforcements have also demonstrated promising outcomes. For example, silk fibroin-polycaprolactone composites have been shown to provide both high tensile strength and excellent biocompatibility, facilitating long-term structural stability without compromising cellular integration. Furthermore, bioresorbable metallic implants, such as magnesium alloy stents, have

emerged as temporary reinforcements that provide mechanical support during the early post-implantation period while gradually degrading to allow for native tissue ingrowth [78].

Another emerging strategy involves the use of dynamic, stress-responsive biomaterials that adapt to physiological forces. Hydrogels with shear-thinning properties have been investigated for their ability to provide localized biomechanical support while enabling cellular remodeling. These materials, when integrated with cell-laden bioinks, have demonstrated potential in reinforcing airway structures while promoting native tissue regeneration. Additionally, 4D bioprinting techniques, which enable scaffold materials to undergo programmed shape transformations in response to environmental stimuli, are being explored as a means to create adaptive tracheal constructs that dynamically respond to respiratory mechanics [77–79].

5.3. Host-graft interactions and immunological challenges

A major barrier to the clinical success of bioengineered tracheal grafts is the host immune response. The interaction between the implanted graft and the host immune system dictates the extent of inflammation, fibrosis, and long-term functionality of the engineered tissue. Ideally, a graft should integrate seamlessly into the recipient's tissue without eliciting excessive inflammatory reactions that could lead to graft rejection or failure. However, the introduction of foreign biomaterials and cellular components often triggers immune responses that compromise graft viability.

5.3.1. Inflammation, fibrosis, and macrophage-driven rejection

Inflammation is an immediate response following graft implantation and is mediated by immune cells such as macrophages, neutrophils, and T lymphocytes. The type of immune response largely depends on the graft composition, surface properties, and degradation kinetics. Macrophages, in particular, play a central role in graft acceptance or rejection, with their polarization into either pro-inflammatory M1 or pro-regenerative M2 phenotypes determining the healing outcome. Persistent M1-dominated inflammation leads to excessive cytokine release, increased fibrosis, and eventual graft failure, whereas a transition to an M2 phenotype promotes tissue remodeling and integration [80].

The fibrotic response is another major concern, as excessive extracellular matrix deposition can lead to airway stenosis, limiting airflow and reducing graft function. Studies have shown that decellularized scaffolds with residual immunogenic components trigger stronger fibrotic reactions, while fully synthetic scaffolds with poor bioactivity can cause chronic low-grade inflammation. Strategies to minimize fibrosis include optimizing scaffold surface topography to modulate immune cell adhesion, functionalizing materials with bioactive peptides to promote controlled immune responses, and using anti-fibrotic agents such as decorin or pirfenidone to regulate excessive collagen deposition [81].

Another immunological challenge is the potential for foreign body reactions in response to synthetic and hybrid scaffolds. Biomaterial surface modifications, such as the incorporation of zwitterionic coatings or polyethylene glycol (**PEG**)-based hydrogels, have been explored to reduce immune cell adhesion and minimize adverse immune responses. Additionally, dynamic immune-modulatory biomaterials that release anti-inflammatory cytokines in response to inflammatory signals have demonstrated promising results in mitigating adverse host reactions [82].

5.3.2. Regenerative immunomodulation for scaffold acceptance

Immunomodulation strategies are being increasingly investigated to shift the immune response toward a regenerative, rather than pro-inflammatory, state. One approach involves pre-seeding scaffolds with immunomodulatory cells, such as MSCs or regulatory T cells (**Tregs**), which have been shown to suppress excessive inflammation and promote tolerance to implanted grafts. MSC-derived exosomes carrying immunoregulatory factors, such as IL-10 and TGF-β, have been used to modify macrophage polarization, shifting them toward a regenerative phenotype [83].

Another promising approach involves the local delivery of immunomodulatory molecules, such as IL-4 and IL-13, which promote M2 macrophage polarization and facilitate tissue repair. Encapsulation of these cytokines in slow-release nanoparticles enables sustained local immunomodulation, reducing systemic side effects while promoting long-term graft acceptance [83].

Genetic engineering approaches have also been explored to enhance graft immune compatibility. CRISPR-Cas9-mediated knockdown of major histocompatibility complex (MHC) molecules in donor-derived cells can reduce the risk of immune rejection. Similarly, synthetic biology techniques allow for the design of immune-evasive biomaterials that dynamically respond to inflammatory stimuli by releasing therapeutic agents that suppress excessive immune activation [84].

Addressing host-graft interactions through regenerative immunomodulation is crucial for the clinical translation of artificial tracheas. Future research should focus on refining biomaterial design, optimizing immune-modulatory therapies, and integrating advanced genetic and cellular engineering techniques to enhance scaffold acceptance and improve long-term graft functionality [83,84].

6. Preclinical and clinical advancements in artificial trachea development

6.1. Animal models for tracheal replacement

6.1.1. Pigs, rabbits, ferrets: advantages and limitations in preclinical testing

Animal models play a pivotal role in the evaluation of bioengineered tracheal constructs, providing critical insights into graft integration, immunogenicity, vascularization, and long-term functionality. The selection of an appropriate animal model is influenced by multiple factors, including anatomical similarity to the human trachea, respiratory biomechanics, and the ability to replicate post-implantation complications such as stenosis, infection, and immune rejection. While no single model perfectly recapitulates human tracheal physiology, pigs, rabbits, and ferrets have emerged as leading models for preclinical tracheal replacement research, each with unique advantages and limitations [85].

Pigs are considered one of the most translationally relevant models due to their airway dimensions, mechanical properties, and respiratory physiology, which closely resemble those of humans. The porcine trachea exhibits a segmental vascular supply and cartilage ring distribution similar to the human airway, making it ideal for evaluating scaffold integration and biomechanical performance. Long-term survival studies in pigs have demonstrated that bioengineered constructs undergo progressive epithelialization and vascularization, mimicking human airway healing responses. However, the use of pigs in preclinical research presents significant challenges, including high costs, the need for advanced surgical expertise, and the risk of graft rejection in allogeneic transplantation models. Moreover, while the porcine immune system shares similarities with humans, discrepancies in inflammatory responses necessitate caution when extrapolating findings to clinical applications [86].

Rabbits are frequently employed in tracheal tissue engineering research due to their affordability, ease of handling, and rapid tissue regeneration capacity. The small airway size of rabbits facilitates

high-throughput testing of different biomaterial formulations, enabling rapid screening of scaffold designs and biocompatibility. However, a major limitation of rabbit models is the discrepancy in cartilage composition and rigidity compared to humans. The rabbit trachea is more flexible and less prone to calcification, which may lead to overestimation of graft efficacy in biomechanical assessments. Additionally, the heightened regenerative ability of rabbit tissues may mask long-term complications such as stenosis and delayed epithelialization, making it challenging to predict clinical outcomes accurately [85].

Ferrets have gained increasing attention as an alternative model for airway reconstruction due to their unique respiratory physiology and susceptibility to airway remodeling. Ferret tracheas exhibit a well-defined mucociliary clearance system, closely resembling the human airway in terms of epithelial regeneration and immune response. This makes ferrets an excellent model for studying host-graft interactions, particularly in the context of epithelialization and mucosal integration. However, the limited availability of ferrets for biomedical research and their smaller airway diameter restrict the scalability of experimental approaches. Additionally, ferrets require specialized care and handling, which may pose logistical challenges in large-scale preclinical studies [85,86].

6.1.2. Evaluation of long-term survival and functional integration

Beyond species selection, the evaluation of long-term survival and functional integration of bioengineered tracheal constructs remains a critical aspect of preclinical research. Standardized assessment criteria include epithelial regeneration, neovascularization, biomechanical stability, and immune response modulation. Advanced imaging techniques, such as contrast-enhanced micro-CT and dynamic fluoroscopy, have been employed to monitor airway patency and vascular integration in real time. Additionally, functional respiratory testing, including lung function assessments and airflow resistance measurements, provides quantitative insights into graft performance under physiological conditions [87].

Despite significant progress, preclinical models still have inherent limitations in replicating human airway pathophysiology, particularly in the context of chronic airway diseases and age-related tissue remodeling. Future research should focus on refining animal models by incorporating comorbid conditions such as chronic inflammation, fibrosis, and infection to better predict clinical outcomes. Moreover, the integration of computational simulations with in vivo studies may enhance predictive accuracy and facilitate patient-specific graft design. As preclinical research continues to evolve, the convergence of advanced bioengineering techniques, immunological insights, and translational modeling will be instrumental in bridging the gap between experimental tracheal grafts and clinical application [88].

6.2. Clinical trials and human applications

The translation of bioengineered tracheal grafts into clinical practice remains a formidable challenge, requiring rigorous evaluation through clinical trials to assess their safety, efficacy, and long-term functionality. Over the past two decades, several pioneering studies have investigated the use of engineered tracheal grafts in human patients, with mixed outcomes. While some cases have demonstrated promising graft integration and airway patency, others have encountered complications such as graft stenosis, infection, and immune rejection, underscoring the need for further refinements in clinical translation [89].

6.2.1. Current clinical studies of engineered tracheal grafts

Several clinical trials and case reports have explored different approaches to tracheal tissue engineering, ranging from decellularized allografts to fully synthetic scaffolds seeded with autologous cells. Decellularized tracheal matrices have been tested in small patient cohorts, showing initial success in structural stability and host integration. However, long-term follow-up data suggest that incomplete revascularization and delayed epithelialization remain major obstacles, often leading to graft failure. Similarly, synthetic polymer-based grafts, including those reinforced with 3D-printed scaffolds, have been implanted in select cases but have demonstrated variable outcomes due to mechanical instability and host immune response [89].

One of the most notable cases of bioengineered tracheal transplantation involved a patient receiving an autologous stem cell-seeded synthetic scaffold. Despite early signs of epithelial regeneration, the graft eventually failed due to chronic inflammation and fibrosis, emphasizing the importance of optimizing immune compatibility and vascularization in future designs. Recent trials have focused on integrating pre-vascularization strategies and immunomodulatory therapies to improve graft survival and reduce adverse events [90].

6.2.2. Outcomes, complications, and future refinements in clinical translation

The major limitations observed in clinical applications of engineered tracheal grafts include insufficient vascularization, inadequate epithelial coverage, and biomechanical mismatch with native tissue. The absence of a robust microvascular network often results in ischemic necrosis, impairing long-term graft viability. To address this, recent efforts have investigated the incorporation of angiogenic growth factors and pre-vascularized grafts to enhance blood supply post-implantation [91].

Complications such as stenosis and restenosis remain significant challenges, particularly in long-segment tracheal replacements. Studies suggest that optimizing scaffold porosity and mechanical properties can mitigate airway collapse while promoting cellular infiltration. Additionally, the role of immunosuppressive therapy in preventing graft rejection is being actively explored, with novel strategies including localized delivery of anti-inflammatory cytokines and biomaterial modifications to reduce immune activation [18].

Looking forward, the refinement of bioengineered tracheal grafts will likely involve personalized medicine approaches, leveraging patient-derived cells and computational modeling to design custom implants with enhanced compatibility. The integration of bioprinting technologies and smart biomaterials capable of responding to physiological cues represents a promising avenue for improving clinical outcomes [18,91].

6.2.3. Ethical considerations and regulatory hurdles in artificial trachea transplantation

The clinical translation of artificial trachea technology is subject to significant ethical and regulatory scrutiny. One of the primary concerns involves patient safety, as the long-term effects of bioengineered grafts remain poorly understood. Ethical considerations also extend to the use of stem cells, particularly in cases involving genetically modified or embryonic-derived cell sources. Regulatory agencies, including the FDA and EMA, require extensive preclinical validation before approving human trials, necessitating robust experimental evidence of safety and efficacy [92].

Regulatory hurdles include stringent requirements for Good Manufacturing Practice (**GMP**) compliance in scaffold fabrication, cell sourcing, and clinical-grade bioreactor systems. The variability in patient responses further complicates the approval process,

emphasizing the need for standardized protocols and multicenter clinical trials to establish reproducibility and scalability [93].

As artificial trachea transplantation moves closer to widespread clinical adoption, interdisciplinary collaboration among biomedical engineers, clinicians, regulatory bodies, and ethicists will be crucial in ensuring the safe and effective implementation of this transformative technology.

7. Future directions and translational strategies

7.1. Personalized medicine and AI-driven tracheal reconstruction

The integration of personalized medicine and artificial intelligence (**AI**) into tracheal tissue engineering represents a paradigm shift in the development of patient-specific airway replacements. Personalized medicine approaches leverage genomic, proteomic, and patient-specific anatomical data to optimize biomaterial selection, scaffold design, and cellular therapies, ensuring improved graft compatibility and functionality. AI-driven methodologies, particularly in the realm of machine learning and computational modeling, are revolutionizing scaffold fabrication, predictive modeling, and surgical planning for artificial trachea transplantation [94].

7.1.1. Artificial intelligence for patient-specific 3D scaffold design

Advancements in 3D bioprinting and computational modeling have facilitated the generation of anatomically precise, patient-specific tracheal constructs. AI-driven algorithms, particularly deep learning-based image processing techniques, enable the rapid segmentation of medical imaging data, such as computed tomography (**CT**) and magnetic resonance imaging (**MRI**) scans, to generate customized 3D-printed scaffolds that conform to a patient's unique airway geometry. By integrating finite element analysis (**FEA**), AI can predict the mechanical performance of scaffold designs, optimizing structural parameters such as porosity, elasticity, and degradation kinetics to enhance graft stability and integration [95].

Moreover, generative adversarial networks (**GANs**) have been employed to simulate patient-specific variations in airway biomechanics, assisting in the development of tracheal scaffolds that maintain functional integrity under physiological stress. These AI-assisted techniques reduce the trial-and-error approach traditionally associated with scaffold optimization, significantly accelerating the translational timeline for engineered tracheal grafts [95].

7.1.2. Machine learning for predictive graft integration modeling

Machine learning algorithms are increasingly being utilized to predict graft-host integration outcomes, facilitating the identification of potential complications before clinical implantation. By analyzing large datasets of preclinical and clinical graft performance, AI models can predict factors such as neovascularization potential, immune response likelihood, and epithelialization efficiency. This predictive capability allows for real-time modifications in scaffold composition and cellular seeding strategies, ultimately enhancing long-term graft viability.

Additionally, AI-driven biomaterial selection processes have been developed to match scaffold compositions with patient-specific regenerative profiles. By integrating multi-omics data—including transcriptomics, metabolomics, and proteomics—machine learning models can identify optimal biomaterial formulations that promote individualized tissue healing while minimizing fibrosis and immune rejection [96].

Future advancements in AI and personalized medicine will likely involve the convergence of in silico modeling with real-time bioprinting technologies, enabling dynamic adaptation of scaffold designs based on intraoperative data. Furthermore, AI-assisted robotic surgical platforms may facilitate the precise placement of engineered tracheal grafts, reducing intraoperative complications and improving post-surgical outcomes. As AI-driven approaches continue to evolve, their integration into tracheal tissue engineering holds immense potential to revolutionize personalized airway reconstruction and improve patient-specific treatment strategies [97].

7.2. Next-generation bioengineered tracheas

The next frontier in artificial trachea development lies in the design of bioengineered constructs that not only mimic the native airway's structural and functional properties but also actively respond to dynamic physiological conditions. Smart biomaterials and bioadaptive scaffolds represent transformative innovations in this field, offering real-time monitoring, self-healing capabilities, and enhanced long-term integration with host tissues [98].

7.2.1. Smart biomaterials with real-time In vivo monitoring capabilities

Advances in biomaterial science have enabled the development of smart scaffolds embedded with biosensors that provide real-time data on graft integration, inflammation, and mechanical stability. These bioengineered constructs incorporate flexible electronic sensors and microfluidic channels capable of detecting changes in pH, oxygenation, and inflammatory cytokine levels, allowing for early intervention in case of complications such as graft stenosis, infection, or airway collapse [99].

Recent studies have demonstrated the feasibility of wireless, bioresorbable electronic sensors integrated into biodegradable tracheal grafts, enabling continuous in vivo monitoring without the need for secondary surgeries. Additionally, electroactive scaffolds composed of conductive polymers, such as polypyrrole and graphene-based composites, have shown potential for modulating cellular behavior through controlled electrical stimulation, accelerating epithelialization and vascularization. The ability to integrate these sensing and stimulation systems into bioengineered tracheas may significantly improve clinical outcomes by enabling precision-guided postoperative care [99].

7.2.2. Self-healing and bioadaptive materials for long-term airway support

The mechanical and biological stability of engineered tracheal grafts is critical for their long-term success. Self-healing biomaterials, inspired by the regenerative properties of natural tissues, have emerged as a promising strategy to enhance graft durability. Hydrogels and elastomeric polymers infused with dynamic covalent bonds or supramolecular interactions enable scaffolds to repair microdamage autonomously, preserving their mechanical integrity over extended periods [98].

Bioadaptive materials take this concept further by dynamically responding to physiological stimuli, adjusting their mechanical properties in response to airway pressures and breathing dynamics. Shape-memory polymers and 4D-printed scaffolds, for example, can undergo controlled morphological changes, ensuring that tracheal grafts maintain optimal airway patency under varying physiological conditions. These materials not only enhance mechanical resilience but also reduce the risk of restenosis and graft failure by adapting to patient-specific airway forces.

Another critical advancement in bioadaptive tracheal engineering is the incorporation of mechanotransductive elements that convert mechanical signals into biochemical responses. Materials engineered to release pro-regenerative factors in response to mechanical stress have been shown to promote tissue integration and

chondrogenesis, creating a feedback loop that strengthens the graft over time [98].

As research in smart biomaterials and bioadaptive scaffolds progresses, future studies should focus on optimizing material biocompatibility, degradation kinetics, and integration with existing monitoring technologies. The convergence of real-time monitoring, autonomous healing, and adaptive biomechanics holds the potential to revolutionize tracheal reconstruction, ushering in an era of truly intelligent airway replacements that dynamically interact with the host environment to ensure long-term function and patient survival [98,99].

7.3. Clinical and commercialization pathways

The transition of bioengineered tracheas from laboratory success to routine clinical use represents one of the most formidable challenges in regenerative medicine. While significant progress has been made in preclinical and early clinical trials, widespread adoption of artificial tracheas requires overcoming regulatory, logistical, and commercial hurdles. Establishing standardized manufacturing processes, ensuring regulatory compliance, and demonstrating long-term efficacy and safety are key components in advancing these technologies to clinical practice [100].

7.3.1. Bridging laboratory success to widespread clinical adoption

Despite promising results from laboratory research, translating engineered tracheal grafts into reliable clinical solutions necessitates rigorous validation through multicenter clinical trials. To date, only a limited number of patients have received bioengineered tracheal implants, with outcomes varying significantly due to inconsistencies in graft design, vascularization strategies, and immune response management. The lack of standardized clinical protocols remains a barrier to large-scale implementation [101].

One of the most pressing challenges is ensuring long-term graft functionality in diverse patient populations. Clinical studies must include extended follow-up periods to evaluate key parameters such as airway patency, mucociliary function, and graft integration. Additionally, collaboration between tissue engineers, thoracic surgeons, and regulatory agencies is essential for defining standardized metrics for success and optimizing surgical techniques for tracheal implantation [102].

Ethical considerations also play a pivotal role in clinical translation, particularly in selecting patient populations for early trials. While artificial trachea transplantation holds immense potential for patients with severe airway defects, stringent inclusion criteria must be established to ensure patient safety. Ethical guidelines should also address concerns related to the use of genetically modified cells, immunosuppressive therapy, and the long-term implications of implanted biomaterials [101,102].

7.3.2. Industrial-scale biomanufacturing of artificial tracheas

For engineered tracheal grafts to reach widespread clinical use, scalable and cost-effective biomanufacturing strategies must be established. Current tissue engineering approaches, including 3D bioprinting and decellularized matrix fabrication, require highly specialized equipment and labor-intensive processes, limiting their scalability. Industrial-scale production must incorporate automation, quality control systems, and reproducible cell-seeding techniques to ensure batch-to-batch consistency [102].

Bioreactor-based culture systems have emerged as a promising solution for large-scale tissue manufacturing. These systems provide controlled environments for cell expansion, differentiation, and extracellular matrix deposition, enabling the production of structurally and functionally robust tracheal grafts. Dynamic perfusion bioreactors, in particular, facilitate uniform oxygenation and nutrient distribution within engineered tissues, enhancing their viability and mechanical stability [101,108].

Regulatory approval for industrial-scale manufacturing also necessitates compliance with GMP standards. Ensuring GMP-compliant production involves rigorous quality assurance testing, including sterility assessments, mechanical property evaluation, and immunogenicity screening. Regulatory agencies such as the FDA and EMA require comprehensive safety and efficacy data before approving bioengineered tissues for human implantation, necessitating extensive preclinical and clinical validation [108].

Another critical aspect of commercialization is cost-effectiveness. The high costs associated with tissue engineering and scaffold fabrication pose significant barriers to widespread adoption. Innovations in biomaterial sourcing, streamlined bioprinting techniques, and decentralized manufacturing facilities may help reduce costs while maintaining product quality. Additionally, public-private partnerships and government funding initiatives can play a crucial role in accelerating commercialization by supporting translational research and facilitating early-stage clinical trials [102].

As the field of tracheal tissue engineering continues to evolve, strategic collaborations between academia, industry, and regulatory bodies will be essential for advancing bioengineered tracheas from experimental prototypes to life-saving clinical interventions. Addressing scalability, regulatory approval, and cost-efficiency will be critical in making engineered tracheal grafts accessible to patients worldwide, ultimately transforming the landscape of airway reconstruction and regenerative medicine.

8. Conclusion

The field of artificial trachea engineering has witnessed remarkable advancements in biomaterial science, cellular therapies, and biofabrication techniques, paving the way for next-generation tracheal replacements with improved biocompatibility, mechanical integrity, and functional integration. However, significant scientific and clinical challenges remain unresolved, including achieving long-term vascularization, ensuring robust epithelialization, mitigating immune rejection, and maintaining biomechanical stability over extended periods. The translation of bioengineered tracheas from experimental success to routine clinical application necessitates a strategic roadmap that integrates multidisciplinary collaborations, regulatory standardization, and scalable biomanufacturing solutions. Future research should focus on optimizing patient-specific scaffold designs using AI-driven modeling, advancing real-time monitoring technologies for graft integration, and refining immunomodulatory approaches to enhance host acceptance. Furthermore, the establishment of multicenter clinical trials, alongside industrial partnerships, will be critical in accelerating commercialization and ensuring widespread clinical adoption. As these innovations converge, artificial trachea engineering is poised to redefine airway reconstruction, offering transformative solutions for patients with complex tracheal defects and advancing the broader field of regenerative medicine.

Ethical approval

The First Hospital of Jilin University Animal Experimental Ethics Committee(No.2023−0639, Approval Date: 2023-09-07).

Data and materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Author contributions

Conceptualization: Wei SX. Data curation: Wei SX and Liang Y. Resources: Wei SX and Zhang AL. Writing - original draft: Wei SX and Zhang AL. Writing - review & editing: Zhang AL.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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