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Review Article

Reconstructing the Injured Lung: A Systems-Regeneration Framework Integrating Pulmonary Precursor Cells, Mitochondrial Therapeutics, and Organ-Specific Nano-Organopeptidic Biologics

Mike KS Chan[1,2,3], Michelle BF Wong[1,2], Krista Casazza[4] and Jonathan RT Lakey[2,4*]

[1]*European Wellness Academy, Klosterstrasse, Edenkoben, Germany*

[2]*European Wellness BioMedical Group, Klosterstrasse, Edenkoben, Germany*

[3]*Lincoln University College, Selangor, Malaysia*

[4]*University of California, Irvine, Department of Surgery and Biomedical Engineering, Irvine CA, USA*

***Corresponding author:** Jonathan RT Lakey, European Wellness BioMedical Group, Klosterstrasse, Edenkoben, Germany, University of California, Irvine, Department of Surgery and Biomedical Engineering, Irvine CA, USA.

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Abstract

Acute and chronic lung diseases remain major causes of morbidity and mortality despite advances in supportive care, anti-inflammatory therapy, antifibrotic treatment, and transplantation. A central limitation of current approaches is that they can attenuate injury or slow disease progression but rarely restore functional pulmonary tissue through regeneration. Lung regeneration requires coordinated restoration of regionally specified epithelial lineages, mitochondrial competence, immune resolution, pulmonary microvasculature, and extracellular-matrix homeostasis; disruption of these interdependent processes can instead produce lineage arrest, persistent inflammation, vascular dysfunction, and fibrosis. This review develops a systems-regeneration framework in which pulmonary repair is approached through three complementary therapeutic domains. Pulmonary Precursor/Progenitor Cells (PSCs) provide a candidate cellular substrate for regionally appropriate epithelial reconstruction, whereas mitochondria-directed therapeutics, including Mito Organelle (MO) biologics, are proposed to address metabolic and organelle-quality-control constraints that limit endogenous and transplanted cell function. Nano-Organ Peptides (NOPs) represent a third candidate modality intended to provide tissue-contextual signals capable of modulating epithelial, vascular, immune, and matrix responses. Importantly, tissue provenance alone does not establish biological specificity, and these modalities require product-specific demonstration of molecular identity, target engagement, potency, biodistribution, and regenerative activity. Within this framework, the European Wellness (EW) platform provides a hypothesis-driven translational architecture integrating PSCs, MO biologics, and organ-derived NOPs as mechanistically distinct but potentially complementary interventions. Current pulmonary evidence for this integrated platform remains preliminary; its principal significance is therefore not demonstration of clinical efficacy, but establishment of a testable strategy for addressing nonredundant regenerative bottlenecks. Translation will require rigorous molecular characterization, mechanism-linked potency assays, factorial testing of individual and combined components, validation in human-relevant pulmonary models, and ultimately controlled clinical evaluation. The decisive test of this approach will be whether coordinated intervention can reproducibly restore structurally integrated and physiologically functional pulmonary tissue rather than merely produce isolated biological effects.

Introduction

Acute and chronic lung diseases collectively impose an exceptional global burden because they compromise not only ventilation but also the highly specialized epithelial–endothelial interface required for oxygen uptake, carbon dioxide elimination, immune defense, and systemic metabolic homeostasis [1]. Chronic Obstructive Pulmonary Disease (COPD) alone affects more than 400 million people and remains among the leading causes of death worldwide [2]. Acute Respiratory Distress Syndrome (ARDS) continues to cause substantial mortality and long-term disability despite improvements in lung-protective ventilation, prone positioning, fluid management, and critical care [3]. Idiopathic Pulmonary Fibrosis (IPF), characterized by progressive and largely irreversible remodeling of the distal lung [4] and BronchoPulmonary Dysplasia (BPD), which disrupts alveolar and vascular development in extremely preterm infants [5] each have substantial adverse effects on respiratory health across the life course. Severe viral and bacterial pneumonias may likewise leave persistent epithelial, endothelial, and fibrotic abnormalities after pathogen clearance, and lung transplantation, although lifesaving for selected patients with end-stage disease, remains limited by donor-organ scarcity, ischemia–reperfusion injury, alloimmune injury, and chronic lung allograft dysfunction [6]. While these disorders display significant heterogeneity in age of onset, initiating insult, and anatomical distribution, they clinically converge in the lost functional capacity related to the lung damage which becomes unable to be preserved of restored in terms of tissue architecture and regional gas-exchange. Current therapies predominantly stabilize physiology or slow disease progression without the ability to restore or regenerate functional lung tissue. In ARDS, management remains largely supportive and is directed toward reducing ventilator-associated injury, maintaining oxygenation, treating the precipitating cause, and supporting other failing organs [7]. No pharmacologic intervention reliably reconstructs the damaged alveolar–capillary barrier [8]. In COPD, bronchodilators, inhaled anti-inflammatory therapies, pulmonary rehabilitation, oxygen supplementation, biologic agents in selected inflammatory endotypes, and bronchoscopic interventions can improve symptoms, exercise capacity, or exacerbation risk, but they do not reliably replace destroyed alveoli or restore the small-airway architecture lost through emphysema and chronic remodeling [9]. Antifibrotic therapies can slow functional decline in IPF and other progressive pulmonary fibrotic disorders, yet they do not reverse established scar formation or rebuild normal alveolar units [10]. Lung transplantation remains the definitive replacement option for selected end-stage diseases, but it substitutes the organ rather than inducing endogenous repair and introduces new risks related to immunosuppression, rejection, infection, and chronic allograft dysfunction [11]. Similarly, contemporary management of BPD emphasizes prevention, ventilatory optimization, nutrition, oxygen titration, and treatment of associated cardiopulmonary complications, but no established therapy consistently reinitiates normal alveolarization and pulmonary microvascular development [12]. The therapeutic limitations of conventional approaches reflect the biological complexity of the respiratory system, which is not a homogeneous epithelial surface but a regionally organized organ comprising tracheal, bronchial, bronchiolar, alveolar, vascular, stromal, and immune compartments. Each compartment of the respiratory system is maintained by distinct resident cell lineages and local signaling niches [13].

Under homeostatic conditions, much of the adult pulmonary epithelium is relatively quiescent14. After injury, however, region-specific facultative progenitors are rapidly recruited to proliferate, migrate, and differentiate [14]. Basal cells contribute to proximal airway repair; club and other secretory-cell populations participate in bronchiolar regeneration; and Alveolar Type 2 (AT2) cells, including specialized WNT-responsive alveolar epithelial progenitors, expand and differentiate toward alveolar type 1 cells to restore the distal gas-exchange surface [15,16]. Human distal airways also contain secretory progenitor populations with regenerative properties that differ from those characterized in animal models, emphasizing the need to define human-specific regenerative biology rather than extrapolating directly from experimental models [17]. Notably, resident epithelial progenitors do not regenerate the lung autonomously [18], rather their survival and lineage decisions depend on reciprocal communication with fibroblasts and other mesenchymal populations, endothelial cells, pericytes, macrophages, lymphocytes, extracellular matrix components, and local metabolic signals. Mesenchymal niches supply Wingless-Related Integration (WNT), Fibroblast Growth Factor (FGF), bone morphogenetic protein (BMP), Transforming Growth Factor Beta (TGF-β), Extracellular Matrix (ECM), and mechanotransducive signals that can promote progenitor expansion and differentiation or, when dysregulated, enforce transitional, metaplastic, or profibrotic states [19]. Endothelial cells provide angiocrine signals and vascular support required to coordinate epithelial repair with reconstruction of the pulmonary capillary bed [20]. Immune populations remove debris and control infection but also generate cytokines and growth factors that determine whether epithelial progenitors complete productive regeneration or become arrested in maladaptive states [21]. The ECM is similarly active, with composition, stiffness, ligand availability, and spatial organization regulating epithelial polarity, cell migration, growth-factor presentation, and fibroblast activation [22]. These reciprocal interactions establish the regenerative niche as a dynamic, multicellular ecosystem in which successful lung repair depends not on the intrinsic properties of epithelial progenitors alone, but on coordinated restoration of cellular, metabolic, vascular, immune, and matrix homeostasis. Despite their etiological heterogeneity, respiratory disorders converge on a failure to restore specialized pulmonary architecture and regional gas-exchange capacity after injury. This review conceptualizes failed lung repair as a system-level regenerative disorder. We propose that next-generation pulmonary therapeutics should

integrate three complementary domains: 1) developmentally and regionally appropriate pulmonary precursor/progenitor cells to provide a cellular substrate for airway or alveolar reconstruction; 2) mitochondrial-directed interventions to restore bioenergetic resilience and organelle quality control; and 3) organ-specific peptide or cell-derived biologics designed to re-establish tissue-contextual communication among epithelial, vascular, immune, and mesenchymal compartments [23]. This framework does not assume that any individual modality is sufficient or clinically validated. Rather, it establishes a mechanistically testable model in which successful lung regeneration emerges from coordinated restoration of cellular identity, mitochondrial competence, vascular integrity, immune resolution, and matrix permissiveness.

The Lung as a Regionally Organized Regenerative Organ

Anatomical and Developmental Compartmentalization: Pulmonary regeneration is intrinsically regional [24]. The conducting airways, distal bronchioles, respiratory bronchioles, alveoli, and pulmonary vasculature each comprise distinct epithelial, mesenchymal, endothelial, immune, and Extracellular Matrix (ECM) niches that differ in cellular turnover, injury susceptibility, and regenerative strategy [1]. Consequently, the adult lung relies not on a universal stem cell population but on anatomically restricted progenitors whose behavior is determined by local developmental programs and microenvironmental signals [2]. Regional identity is established during embryogenesis and remains a fundamental determinant of adult regenerative competence [3]. NKX2-1 is the master regulator of pulmonary epithelial identity, while SOX2 and SOX9 broadly specify proximal and distal epithelial programs, respectively [4]. These transcriptional networks are integrated with conserved developmental pathways (e.g., WNT, FGF, BMP, retinoic acid, Notch, Hippo–YAP/TAZ, and TGF-β) that coordinate progenitor maintenance, epithelial differentiation, branching morphogenesis, and alveolar specification [5]. Many of these pathways are reactivated following injury. Transient activation facilitates regeneration, whereas persistent signaling promotes epithelial plasticity, fibroblast activation, extracellular matrix remodeling, and fibrosis [6]. Accordingly, adult lung repair represents controlled re-engagement of developmental programs rather than recapitulation of embryogenesis [7,8]. Successful regeneration requires timely activation of progenitor populations followed by restoration of mature epithelial identity and tissue architecture. Thus, failure to terminate these developmental programs redirects repair toward chronic remodeling and fibrotic disease.

Principal Endogenous Pulmonary Progenitor Populations: Each anatomical compartment contains specialized progenitor populations responsible for maintaining regional homeostasis. Basal cells serve as the principal stem cells of the proximal airways, generating secretory and multiciliated epithelium following injury, although persistent basal-cell expansion contributes to bronchiolization and metaplasia [9]. Thus, pulmonary regenerative competence is defined not merely by progenitor activation but by restoration of anatomically appropriate mature cell states. This distinction between productive lineage progression and persistent transitional remodeling provides the basis for examining why regenerative programs fail after severe or chronic injury.

Productive Regeneration Versus Maladaptive Repair: Following severe or persistent injury, normally transient epithelial intermediates may instead become arrested, while cross-compartment plasticity can produce metaplastic rather than functional epithelium [10]. Thus, regenerative competence evaluation may be better served by assessing the restoration of regional identity and function, rather than progenitor expansion alone (Table 1).

Table 1: Region-Specific Pulmonary Progenitor Populations in Homeostasis, Injury Repair, and Maladaptive Remodeling*.

Compartment	Progenitor Population / Markers	Physiological role	Injury Response / Maladaptive Fate	Regenerative Relevance
Trachea and proximal conducting airways	**Basal cells** -TP63, KRT5, KRT14, NGFR	Self-renewing airway stem cells that generate secretory and multi-ciliated epithelium and maintain mucociliary barrier integrity.	Rapidly expand and migrate after epithelial injury. Persistent or ectopic activation can produce squamous metaplasia, mucus remodeling, and distal basalization/bronchiolization.	Strong candidate for proximal-airway reconstruction, but therapeutic benefit requires preservation of regional identity and controlled differentiation rather than basal-cell expansion alone.
Bronchiolar and distal conducting airways	**Club and distal secretory progenitors** - SCGB1A1, SCGB3A1; SCGB3A2 in human distal secretory populations	Maintain secretory and epithelial-defense functions and replenish secretory and ciliated lineages; selected distal populations exhibit broader regenerative plasticity after injury.	Expand following toxic, infectious, or epithelial injury. Dysregulated fate can result in secretory/mucous metaplasia, incomplete differentiation, or inappropriate contribution to remodeled distal epithelium.	Potential targets for small-airway regeneration and endogenous repair; human-specific distal progenitor biology should be distinguished from murine club-cell paradigms.

Bronchioalveolar junction and human respiratory airways	**Bronchioalveolar / respiratory-airway progenitors** - SCGB1A1/SFTPC in murine BASCs; SCGB3A2-associated signatures in human respiratory-airway secretory cells	Provide regionally restricted progenitor activity at the airway–alveolar interface and can contribute to distal epithelial repair under defined injury conditions.	Severe injury increases lineage plasticity and recruitment across airway–alveolar boundaries; persistent or misdirected expansion may contribute to bronchiolization or inappropriate lineage allocation.	Potential cellular bridge between airway and alveolar repair, but species differences and precise human lineage relationships require careful definition before therapeutic extrapolation.
Alveolar compartment	**AT2 and WNT-responsive alveolar progenitors** - SFTPC, SFTPB, ABCA3, NAPSA; AXIN2/TM4SF1-enriched progenitor subsets	Maintain surfactant homeostasis, self-renew, and generate AT1 cells required for restoration of the gas-exchange surface.	Expand after alveolar injury and transiently enter intermediate states during AT1 differentiation. Persistent stress, senescence, or failure of lineage progression produces KRT8-high transitional arrest and profibrotic signaling.	Principal cellular target for alveolar regeneration. Therapeutic success requires preservation of AT2 identity, functional maturation, and completion of AT2-to-AT1 differentiation rather than proliferation alone.
Severely injured/remodeling distal lung	**Injury-induced transitional and cross-compartment progenitors** - KRT8, CLDN4, SFN transitional states; KRT5/TP63 in migratory basal-like populations	Normally provide transient intermediates during alveolar differentiation or emergency epithelial coverage following extensive injury.	Failure to resolve transitional states produces senescence-associated and profibrotic signaling; persistent airway-derived basal-like cells can generate metaplastic bronchiolization rather than functional alveolar epithelium.	Demonstrates that cellular plasticity is context-dependent and not intrinsically regenerative. Therapies should promote resolution toward anatomically appropriate mature epithelium while preventing persistent transitional or metaplastic states.

Note*: Pulmonary progenitor activity is anatomically and contextually restricted. Marker expression identifies candidate cellular states but does not independently establish lineage potential or therapeutic competence. Injury-induced plasticity may support repair or drive maladaptive remodeling depending on injury severity, niche signaling, and completion of lineage maturation. Accordingly, regenerative strategies should be evaluated by restoration of regionally appropriate mature epithelial identity and function, rather than progenitor expansion alone.

Why Lung Regeneration Fails

Although the adult lung possesses substantial regenerative capacity, successful repair depends on coordinated interactions among epithelial progenitors, stromal cells, pulmonary endothelial cells, immune populations, and the Extracellular Matrix (ECM). Severe, repetitive, or age-related injury can disrupts this coordination, converting an initially adaptive repair response into a self-sustaining cycle of epithelial dysfunction, persistent inflammation, endothelial dysfunction, and fibrosis. Consequently, regenerative failure reflects dysfunction of the broader regenerative niche rather than impairment of a single progenitor population [25].

Epithelial Lineage Arrest: Regeneration depends on the ability of AT2 cells to self-renew and differentiate into mature AT1 cells [26]. Following injury, AT2 cells transiently adopt KRT8-positive transitional states that facilitate alveolar regeneration; however, persistent of these cells, characterized by activation of p53, TNFα/NF-κB, senescence-associated, and other stress- response programs, is associated with impaired epithelial differentiation and fibrotic remodeling [27]. Rather than restoring functional alveolar epithelium, these persistent transitional cells contribute to chronic remodeling and fibrosis.

Metabolic Failure: Mitochondrial homeostasis is increasingly recognized as an important determinant of AT2-cell regenerative competence [28]. Loss of oxidative phosphorylation, impaired mitophagy, and excessive ROS compromise mitochondrial ATP production and AT2-cell functions required for alveolar repair, including proliferation, differentiation, and surfactant homeostasis [29]. Impaired NAD^+ homeostasis further compromises AT2-cell progenitor function and regenerative capacity [30]. Mitochondrial injury can simultaneously amplify inflammatory and profibrotic signaling through the release of mitochondrial damage-associated molecular patterns, particularly mtDNA [31]. Restoration of mitochondrial quality control improves epithelial survival and regenerative capacity in experimental lung injury, underscoring metabolic competence as an important requirement for effective repair [28].

Failure of Niche Resolution: Persistent activation of inflammatory macrophages, monocytes, and neutrophils amplify alveolar epithelial injury [32], whereas endothelial dysfunction impairs angiocrine signaling that supports epithelial progenitor expansion and alveolar regeneration [33]. These abnormalities impair endothelial repair, sustain inflammatory signaling, and reinforce defective AT2-to-AT1 differentiation, thereby limiting restoration of functional alveolar–capillary units [25].

Matrix Remodeling and Aging: Persistent fibroblast activation and excessive ECM deposition transform a transient reparative matrix into a stiff, chronically profibrotic microenvironment. Matrix stiffening activates mechanotransductive pathways, including integrin/FAK, YAP/TAZ, and TGF-β signaling, that stabilize myofibroblast activation and reinforce pathological ECM remodelling [34]. Aging further reduces regenerative reserve through mitochondrial dysfunction, cellular senescence, loss of proteostasis, and immune dysregulation, increasing susceptibility to maladaptive remodeling rather than complete architectural repair [35]. Together, these coupled defects frame regeneration as a problem of coordinated tissue-state restoration rather than correction of an isolated molecular lesion. The critical translational question is therefore whether existing interventions can reconstruct a regeneration-competent pulmonary environment rather than merely modify individual components.

The Pulmonary Regenerative Plateau: Why Current Therapies Remain Incomplete

Current regenerative strategies have substantially advanced pulmonary repair but generally target only one component of the complex biology underlying lung regeneration. Anti-inflammatory and antifibrotic therapies remain foundational for limiting ongoing tissue injury but possess limited capacity to restore damaged lung architecture [36]. Corticosteroids, cytokine-directed biologics, and other immunomodulators effectively suppress inflammation in selected pulmonary diseases [37], whereas antifibrotic agents slow physiological decline in progressive fibrotic lung disorders [38]. However, these therapies replenish depleted AT2 progenitors nor restore mature alveolar architecture or pulmonary microvasculature and therefore function primarily as disease-modifying rather than regenerative interventions. MSCs have been extensively investigated for their immunomodulatory, angiogenic, antimicrobial, and barrier-supportive properties [22]. Increasing evidence indicates that these effects are mediated predominantly through paracrine signaling, Extracellular Vesicles (EVs), and, in some settings, mitochondrial transfer rather than durable engraftment [39]. Although early clinical studies have demonstrated acceptable safety profiles, randomized trials and recent meta-analyses have produced inconsistent efficacy, highlighting persistent challenges related to donor variability, product heterogeneity, manufacturing, potency, dosing, and patient selection [23,24,40,41]. Consequently, MSCs are increasingly viewed as transient modulators of the regenerative niche rather than direct mediators of epithelial reconstruction. Pulmonary epithelial progenitors derived from primary tissue, organoids, or pluripotent stem cells offer a more direct route toward structural replacement, but their efficacy remains constrained by engraftment, lineage maturation, regional specification, and the pathological recipient niche [25,26,42,43]. EVs, biomaterials, and gene-editing approaches address complementary signaling, structural, and genetic constraints but likewise do not independently reconstruct functional alveolar–capillary architecture [27,44]. Mitochondrial-directed therapies represent one of the most promising emerging approaches because mitochondrial dysfunction intersects epithelial regeneration, endothelial integrity, immune activation, and fibroblast persistence [28,45]. Experimental studies of mitochondrial transfer and mitophagy modulation have demonstrated encouraging preclinical activity in lung injury and fibrosis models [46]. Mitochondria-targeted peptides have likewise shown beneficial effects in experimental pulmonary fibrosis models [47]. Restoration of NAD+ homeostasis has also improved alveolar epithelial progenitor function and attenuated fibrosis in experimental models30. However, important questions regarding mitochondrial product characterization, biodistribution, stability and persistence, functional potency, and mechanism of action remain to be resolved before these approaches can be broadly translated clinically [29,48,49]. The resulting translational gap therefore reflects not an absence of biologically active interventions, but the absence of a validated strategy that coordinates structural replacement with restoration of the conditions required for that replacement to survive and function.

Pulmonary Precursor Cells as the Structural Foundation of Regeneration

Pulmonary Precursor/Progenitor Cells (PSCs) represent the structural foundation for regeneration by providing lineage-specific cells capable of restoring damaged airway and alveolar epithelium. Unlike mesenchymal stromal cells, whose principal activity is paracrine immunomodulation, pulmonary PSCs are intended to restore regional epithelial architecture through developmentally appropriate differentiation. Their therapeutic potential therefore depends on maintaining defined pulmonary lineage identity rather than stemness alone. Respiratory epithelial specification is governed by sequential activation of developmental programs culminating in NKX2-1-positive respiratory progenitors, followed by proximal-distal patterning into Sox2-positive proximal and Sox9/Id2-positive distal progenitors that subsequently generate basal, secretory, multi-ciliated, AT2, and AT1 lineages [50]. Consequently, successful regenerative therapies must reproduce these developmental programs and generate populations with defined pulmonary fate rather than rely on heterogeneous stem-cell populations. Several candidate cellular platforms have emerged, including endogenous pulmonary progenitors, primary AT2 cells, airway basal cells, fetal and postnatal lung-derived progenitors, embryonic stem cell- and induced pluripotent stem cell-derived pulmonary progenitors, and organoid-expanded epithelial populations. Each offers distinct advantages but shares common translational barriers, including scalable manufacturing, lineage stability, regional specification, immune compatibility, optimized delivery, and durable integration within injured tissue [51]. Importantly, epithelial engraftment alone is insufficient for functional repair. Transplanted cells must survive within the oxidative and inflammatory environment of the injured lung, integrate with pulmonary endothelium and extracellular matrix, restore surfactant production, participate in alveolar remodeling, and establish long-term interactions with resident

stromal and immune cells [52]. Organoid systems and lung-on-chip technologies therefore serve not only as therapeutic platforms but also as increasingly important models for defining lineage fidelity, epithelial maturation, and mechanism-based potency [50]. Pulmonary PSCs may contribute to regeneration through several complementary mechanisms. Direct epithelial replacement provides the most obvious therapeutic objective; however, accumulating evidence indicates that transplanted pulmonary progenitors may also influence the surrounding regenerative niche through secretion of trophic factors, extracellular vesicles, and regulatory molecules that support endogenous epithelial repair, vascular stabilization, and immune resolution. These indirect effects should be distinguished experimentally from structural engraftment because they require different potency assays and may contribute substantially to therapeutic benefit [51,14]. Accordingly, the translational criterion for pulmonary cell therapy is not stemness per se, but reproducible regional identity, lineage stability, functional maturation, and demonstrable contribution to pulmonary repair (Table 2).

Table 2: Candidate Pulmonary Precursor and Progenitor Cell Platforms for Regenerative Lung Therapy**.

Cell Source	Intended Lineage / Target Compartment	Developmental and Identity Markers	Proposed Mechanism	Evidence Level	Principal Translational Barrier	Required Release Criteria
Primary adult AT2 cells, including progenitor-enriched AT2 subsets	Distal alveolar epithelium; AT2 self-renewal and AT1 generation	SFTPC, SFTPB, ABCA3, NAPSA, EPCAM; progenitor-enriched subsets may include AXIN2/TM4SF1 signatures	Direct replacement of injured AT2 cells; restoration of surfactant production; AT1 differentiation; support of alveolar repair	Preclinical transplantation, lineage-tracing, and organoid evidence	Limited tissue availability; donor variability; phenotype loss during expansion; poor engraftment in fibrotic niches	Viability; pulmonary identity; surfactant processing; organoid formation; controlled AT2-to-AT1 differentiation; transcriptomic stability; absence of persistent stress, senescence, or profibrotic transitional states
Primary airway basal cells	Tracheal and proximal conducting-airway epithelium	TP63, KRT5, KRT14, NGFR, KRT17	Durable airway stem-cell engraftment; generation of secretory and multiciliated epithelium; restoration of mucociliary barrier	Strong organoid and preclinical engraftment evidence	Need for niche access or conditioning; nonuniform delivery; risk of squamous metaplasia or inappropriate distal banalization	Basal-cell purity; clonogenicity; genomic stability; mucociliary differentiation; epithelial barrier function; absence of dysplasia and senescence
Distal airway secretory progenitors	Bronchiolar and respiratory-airway epithelium; selected contribution to distal alveolar repair	SCGB1A1, SCGB3A1/SCGB3A2 and region-specific secretory signatures	Bronchiolar epithelial repair; generation of secretory/ciliated lineages; potential contribution to alveolar regeneration after severe injury	Strong preclinical lineage evidence; human distal secretory progenitors identified in organoid systems	Incomplete standardization of human populations; species differences; uncertain durable alveolar contribution	Compartment-specific identity; organoid-forming capacity; appropriate airway and/or alveolar differentiation; absence of mucous metaplasia, bronchiolization, or aberrant basal expansion
Fetal or postnatal pulmonary progenitors	Airway or alveolar epithelium according to developmental stage and regional source	NKX2-1, SOX2, SOX9, ID2, EPCAM and stage-specific proximal/distal programs	High proliferative capacity; developmentally patterned epithelial reconstruction; potential trophic niche support	Human organoid and preclinical engraftment evidence	Ethical and sourcing constraints; donor variability; incomplete maturation; immunogenicity; ectopic lineage risk	Developmental-stage and source definition; pulmonary identity; lineage restriction; genomic stability; viability; sterility; pathogen screening; maturation and potency assays
ESC/iPSC-derived NKX2-1 pulmonary progenitors	Expandable airway or alveolar progenitors; includes AT2-like and basal-cell derivatives	NKX2-1 with EPCAM/FOXA2 and proximal/distal lineage markers; SFTPC/ABCA3 for alveolar products; TP63/KRT5 for basal derivatives	Scalable generation of defined pulmonary lineages; direct epithelial replacement; gene correction; disease-specific autologous or allogeneic platforms	Extensive differentiation and organoid evidence; preclinical transplantation increasingly developed	Residual pluripotency; off-target thyroid/neural lineages; incomplete maturation; genomic instability; tumorigenicity; manufacturing complexity	Pulmonary-lineage purity; residual pluripotency below validated threshold; genomic stability; off-target lineage exclusion; functional airway/alveolar differentiation; tumorigenicity and gene-editing safety assays where applicable

Organoid-derived pulmonary epithelial progenitors	Airway or alveolar compartment depending on source and culture system	Source-dependent profiles including NKX2-1, SFTPC, ABCA3, TP63, KRT5, SCGB1A1, FOXJ1	Ex vivo expansion while preserving aspects of lineage architecture; transplantation source; mechanism-based potency platform	Strong disease-modeling and preclinical evidence	Product heterogeneity; matrix dependence; incomplete vascular/immune maturation; loss of phenotype after dissociation or cryopreservation	Defined culture system; cellular composition; lineage purity; organoid-forming efficiency; barrier or surfactant function; post-thaw stability and reproducibility
Organ-matched candidate pulmonary precursor preparation	Intended pulmonary regenerative support; exact target lineage must be empirically established	Must be experimentally defined; should not be designated AT2, basal, NKX2-1-positive, or other established progenitor type without direct characterization	Candidate direct replacement, paracrine support, endogenous progenitor activation, or niche modulation depending on product composition	Hypothesis-driven; product-specific pulmonary identity, engraftment, potency, and efficacy require direct validation	Undefined cellular composition, developmental stage, lineage identity, mechanism, biodistribution, and manufacturing reproducibility unless specifically characterized	Source and developmental-stage definition; viable-cell content; single-cell and protein-level identity; clonogenicity; airway/alveolar organoid formation; functional differentiation; genomic stability; sterility; potency; biodistribution; immunogenicity and tumorigenicity

Note*: **Evidence level refers to support for the underlying cell platform, not proof of clinical efficacy in human lung disease. Developmental or anatomical origin alone does not establish therapeutic specificity. Each candidate product requires indication-matched potency assays demonstrating airway or alveolar function, together with validated identity, purity, safety, stability, and biodistribution criteria.

Mitochondrial Dysfunction as a Therapeutic Bottleneck in Lung Regeneration

Mitochondrial competence represents a potentially modifiable bottleneck in pulmonary regeneration because epithelial proliferation and differentiation, endothelial repair, immune-state transitions, and stromal remodeling all impose distinct bioenergetic and organelle-quality-control requirements.

Mitochondria Coordinate Pulmonary Regeneration: AT2 cells are both metabolically active epithelial cells and the principal progenitors responsible for alveolar maintenance. Their ability to self-renew and differentiate into AT1 cells depends upon intact oxidative metabolism, mitochondrial biogenesis, and mitophagy. Experimental studies demonstrate that defective mitochondrial quality control impairs AT2 survival, promotes epithelial lineage arrest, and sustains stress-associated transitional states characteristic of ARDS, COPD, and IPF. Conversely, restoration of mitophagy improves epithelial survival and regenerative capacity following experimental lung injury, establishing mitochondrial quality control as a direct regulator of pulmonary regeneration. [1,2,5] Mitochondrial dysfunction also extends beyond the epithelium. In macrophages, mitochondrial metabolism influences inflammatory activation and resolution, while mitochondrial DNA release activates cGAS-STING and inflammasome signaling that perpetuate lung injury. Pulmonary endothelial cells similarly depend on mitochondrial homeostasis to maintain barrier integrity, vascular permeability, angiocrine signaling, and microvascular repair. Consequently, mitochondrial dysfunction creates a feed-forward cycle in which epithelial injury, vascular leak, hypoxia, and chronic inflammation reinforce one another, progressively reducing regenerative capacity.

Mitochondrial Therapeutics: Recognition of mitochondria as a regenerative target has stimulated development of multiple therapeutic strategies, including mitochondria-targeted antioxidants, NAD^+ augmentation, AMPK-PGC-1α activation, mitophagy modulation, mitochondrial-derived peptides (including MOTS-c and Humanin), extracellular vesicle-mediated metabolic support, and direct mitochondrial transfer. Although these approaches differ mechanistically, they share the common objective of restoring mitochondrial quality control and metabolic resilience rather than simply reducing oxidative stress. Experimental models demonstrate improvements in epithelial survival, endothelial function, and ischemia-reperfusion injury, but most approaches remain preclinical, and questions regarding biodistribution, persistence, target engagement, and optimal therapeutic timing remain unresolved. These observations establish metabolic competence as a potentially independent therapeutic constraint on pulmonary regeneration. However, mitochondrial-directed interventions differ fundamentally in composition and mechanism; intact-organelle transfer, mitochondrial-derived peptides, redox modulators, and organelle fractions should therefore not be treated as mechanistically interchangeable without product-specific characterization.

NOPs as Tissue-Contextual Regenerative Signals

NOPs represent the signaling component of the proposed regenerative framework. Unlike Pulmonary Precursor/Progenitor Cells (PSCs), which provide lineage-specific cellular substrates, or mitochondrial-directed biologics that restore metabolic competence, NOPs are intended to recreate aspects of the tissue microenvironment that coordinates repair. This concept is grounded in the recognition that peptides function as fundamental

mediators of developmental, paracrine, endocrine, immune, and extracellular matrix signaling. Tissue injury profoundly remodels the local peptidome through regulated secretion, extracellular proteolysis, matrix degradation, and inflammatory activation, generating bioactive peptides capable of influencing epithelial differentiation, angiogenesis, immune responses, mitochondrial function, and tissue remodeling. Consequently, organ-derived peptide preparations may provide biologically relevant regenerative signals without requiring viable cells. The biological rationale for organ specificity derives from developmental biology rather than generalized trophic activity. Individual tissues maintain distinct transcriptional, proteomic, and extracellular matrix programs throughout adult life, suggesting that their peptide repertoires may likewise retain tissue-contextual regulatory functions. Within the lung, such signals are hypothesized to support epithelial survival, AT2 progenitor function, barrier restoration, endothelial communication, matrix homeostasis, and resolution of injury. Placental peptides provide a complementary rationale because placental biology integrates immune tolerance, angiogenesis, oxidative stress adaptation, and tissue remodeling. While these concepts are biologically plausible, organ specificity cannot be inferred from tissue origin alone and require direct molecular characterization together with demonstration of pulmonary target engagement. The translational question is therefore not whether endogenous peptides participate in pulmonary repair, but whether an exogenously prepared tissue-derived peptide fraction reproducibly contains defined bioactive species at concentrations capable of producing therapeutically relevant target engagement. Tissue origin provides a hypothesis for biological specificity, not evidence of it. Demonstrating specificity requires compositional definition, comparative activity against unrelated tissue fractions, dose–response relationships, pharmacokinetics, and mechanism-linked pulmonary potency assays. Lung-directed NOPs require peptide sequencing, quantitative proteomics, source-tissue authentication, pharmacokinetic profiling, and mechanism-based potency assays linked to pulmonary regeneration, including AT2 organoid formation, AT2-to-AT1 differentiation, epithelial barrier restoration, endothelial stabilization, macrophage resolution, and extracellular matrix remodeling. These requirements establish the experimental framework needed to determine whether tissue-derived NOP preparations possess reproducible pulmonary biological activity (Table 3).

Table 3: Proposed Organ-Derived Peptide Categories Relevant to Pulmonary Regeneration^ Proposed mechanisms should be interpreted as testable hypotheses unless direct compositional, cellular, animal, or clinical evidence is available for the specific NOP preparation. Evidence supporting the source endogenous signaling biology of the tissue does not establish the composition, potency, lung biodistribution, or therapeutic efficacy of an organ-derived peptide product.

NOP Source	Proposed Bioactive Domains	Principal Pulmonary Targets	Candidate Regenerative Mechanisms	Current Evidence / Maturity	Critical Validation Gap
Lung-/alveolar-derived NOPs	Pulmonary epithelial, developmental, matrix-associated, trophic, and stress-response peptide signals	AT2/AT1 lineage; airway epithelium; epithelial–mesenchymal interface	Proposed support of epithelial survival, progenitor maturation, barrier restoration, surfactant homeostasis, and injury-responsive tissue signaling	Biological rationale supported by pulmonary developmental and peptide signaling biology; product-specific evidence remains early	Peptide identification and quantitative composition; demonstration of preferential pulmonary activity; regional specificity (airway vs alveolar); receptor/pathway engagement; dose–response; pharmacokinetics; disease-specific efficacy
Placenta-derived NOPs	Immunoregulatory, angiogenic, growth-factor-associated, extracellular-matrix, and stress-adaptation signals	Pulmonary endothelium; immune–epithelial interface; injured alveolar niche	Proposed modulation of inflammatory resolution, endothelial repair, microvascular stability, epithelial survival, and fibrotic remodeling	Strong biological rationale from placental immunovascular biology; regenerative effects reported for placenta-derived biologics more broadly, but direct evidence for defined NOP preparations in pulmonary regeneration remains limited	Molecular definition of active peptides; distinction from placental secretomes/EVs; pulmonary biodistribution and target engagement; comparative activity versus lung-derived fractions; controlled pulmonary efficacy studies
Immune-/thymic-derived NOPs	Immune-regulatory and homeostatic peptide signals	Alveolar macrophages; recruited myeloid populations; lymphocytes; epithelial–immune signaling networks	Proposed promotion of inflammatory resolution and restoration of immune homeostasis, potentially reducing persistent inflammatory constraints on epithelial repair	Mechanistic rationale supported by immune–epithelial interactions in lung repair; direct evidence for thymic/immune-derived peptide fractions as pulmonary regenerative agents is limited	Defined peptide composition; identification of immune targets and receptor pathways; demonstration of pro-resolution rather than generalized immunosuppressive activity; pulmonary pharmacodynamics and safety

Mitochondrial-/ metabolic-derived peptide fractions	Mitochondrial proteins/ peptides and metabolic stress-response signals; potentially including mitochondrial-derived signaling peptides depending on preparation	AT2 progenitors; pulmonary endothelium; macrophages; metabolically stressed stromal cells	Proposed modulation of bioenergetic resilience, redox signaling, mitochondrial quality control, stress responses, and organelle-linked inflammatory signaling	Substantial independent evidence supports mitochondrial regulation of pulmonary repair and biological activity of defined mitochondrial-derived peptides; evidence for complex organelle-derived peptide preparations remains product-specific and preliminary	Precise distinction between intact organelles, organelle fractions, and peptide preparations; molecular composition; mitochondrial target engagement; uptake and persistence; mechanism-linked potency; comparative efficacy and safety

European Wellness as an Integrated Platform for Pulmonary Systems Regeneration

The European Wellness (EW) platform integrates three candidate regenerative modalities within a single translational architecture directed at nonredundant constraints on pulmonary repair: pulmonary PSCs as a potential cellular substrate for structural reconstruction, MO biologics as candidate modulators of metabolic competence, and NOPs as proposed tissue-contextual signals influencing epithelial, vascular, immune, and matrix responses. Its scientific rationale therefore resides in the predicted functional complementarity of these modalities rather than in the activity of any single component. A central feature of the EW approach is its emphasis on organ specificity. Pulmonary repair is regionally encoded: airway basal cells, distal secretory progenitors, alveolar type II cells, endothelial populations, and mesenchymal niches possess distinct developmental identities and regenerative functions. EW proposes that cells and molecular fractions derived from defined tissues may retain elements of these developmental, proteomic, and signaling programs. This premise is consistent with established evidence that progenitor competence, secretory phenotype, extracellular-vesicle cargo, and matrix interactions vary according to tissue and developmental origin. Nevertheless, tissue provenance alone cannot establish therapeutic specificity. Direct comparative studies must demonstrate that lung-derived PSCs or NOPs produce pulmonary lineage or functional effects that are not reproduced by unrelated tissue preparations. Accordingly, organ specificity should be treated as an experimentally falsifiable property rather than an intrinsic attribute conferred by anatomical source. A pulmonary preparation would satisfy this criterion only if its molecular identity and biological activity demonstrate preferential engagement of pulmonary lineages or regenerative programs relative to appropriately selected no pulmonary controls. The integration of PSCs, MOs, and NOPs is intended to address a major limitation of conventional regenerative strategies: biologically active therapies are usually developed in isolation despite their dependence on the same injured microenvironment. Pulmonary PSCs may possess appropriate lineage potential yet fail if mitochondrial stress, endothelial dysfunction, inflammation, or fibrotic matrix conditions prevent survival and maturation. MO biologics may improve cellular energetics but cannot independently replace destroyed epithelium. NOPs may modify intercellular signaling but cannot provide durable structural reconstruction. The platform therefore assigns each modality a nonredundant role and predicts that metabolic stabilization and niche conditioning may increase the capacity of pulmonary progenitors to engraft, differentiate, and restore regional architecture.

The platform's central proposition is that structural replacement, metabolic competence, and tissue-contextual signaling constitute distinct but interacting constraints on regeneration. Its value therefore depends on demonstrating that integration produces mechanistically attributable effects beyond those achieved by individual components. The current EW literature provides a broad conceptual and translational foundation spanning organ-specific precursor cells, peptide biology, mitochondrial regulation, and regenerative medicine across several organ systems. However, much of this evidence consists of mechanistic synthesis, exploratory observations, or early translational reports rather than controlled pulmonary studies. Direct evidence defining the composition, target engagement, pharmacology, and efficacy of pulmonary PSC, MO, and NOP preparations remains limited. The platform should therefore be presented as hypothesis-driven and experimentally actionable, not as an established treatment for lung regeneration. The principal contribution of the EW platform is not demonstration of pulmonary efficacy, but the establishment of a testable systems-regeneration framework integrating complementary regenerative modalities.

Translational Priorities and Future Directions

Translation should begin with independent product definition. Pulmonary PSC preparations require validated cellular identity, purity, viability, genomic stability, and lineage-restricted potency. Characterization should establish whether the product contains viable progenitors, tissue fractions, or secreted components and should distinguish airway from alveolar specification. Release assays must predict the intended function, such as organoid formation, surfactant production, mucociliary differentiation, epithelial barrier formation, or alveolar type II-to-type I differentiation. Biodistribution, persistence, immunogenicity, ectopic growth, and tumorigenic potential must also be determined. MO biologics requires compositional and functional resolution. Studies must establish whether preparations contain intact mitochondria, organelle fragments, membranes, proteins, peptides, metabolites, or mixed fractions. If intact organelles are present, membrane integrity, mitochondrial DNA quality, respiratory-chain

activity, oxygen consumption, ATP generation, and respiratory-control ratios are essential release attributes. For non-intact preparations, potency should instead be linked to defined metabolic effects. Uptake, intracellular localization, persistence, mitophagy response, and effects on mitochondrial danger signaling should be evaluated in epithelial, endothelial, immune, and stromal pulmonary populations. NOP development requires peptide-level analytical control. Mass spectrometry, sequence identification, molecular-weight distribution, post-translational modifications, source-tissue authentication, stability, contaminant testing, and batch fingerprinting are required to establish reproducibility. Pharmacokinetics, pulmonary biodistribution, target-cell uptake, and pathway engagement should be defined for each preparation. Potency assays should measure indication-relevant functions, e.g., epithelial maturation, endothelial barrier stabilization, inflammatory resolution, and fibroblast restraint, rather than nonspecific cell proliferation. Direct comparison of lung-, placenta-, and unrelated organ-derived fractions will be necessary to substantiate tissue specificity. Crucially, validation should proceed hierarchically: product identity must precede mechanism, mechanism must precede combination testing, and biological target engagement must precede claims of tissue regeneration. Integrated development should proceed through factorial studies evaluating PSCs, MOs, and NOPs individually, pairwise, and in combination. Human pulmonary organoids, precision-cut lung slices, lung-on-chip systems, and ex vivo perfused lungs can determine whether multimodal treatment improves lineage maturation, mitochondrial competence, vascular integration, or matrix remodeling beyond the effects of individual components. Disease models should be indication-specific and encompass mechanistically distinct contexts such as acute epithelial injury, fibrosis, emphysematous destruction, developmental lung injury, and transplantation-associated ischemia–reperfusion injury.

Conclusions

Failed pulmonary regeneration reflects coupled dysfunction of epithelial lineage progression, mitochondrial competence, immune resolution, vascular integrity, and extracellular-matrix remodeling. Existing therapies can modify individual components of this biology, but durable regeneration ultimately requires restoration of functional airway or alveolar–capillary architecture. A systems-regeneration model therefore provides a rational basis for combining complementary modalities with distinct functions: pulmonary PSCs as a cellular substrate for structural reconstruction, mitochondria-directed biologics as modulators of metabolic competence, and organ-derived NOPs as candidate tissue-contextual signals. The central hypothesis is not that combination therapy is intrinsically superior, but that correction of nonredundant regenerative bottlenecks may permit effects that isolated interventions cannot achieve. The EW platform provides a structured and experimentally testable implementation of this hypothesis (Figures 1-3) [23], but its pulmonary evidence remains preliminary. Ultimately, the validity of this systems-regeneration framework will be determined not by generalized biological activity or the activity of individual components, but by whether mechanistically defined interventions can reproducibly restore structurally integrated, physiologically functional pulmonary tissue (Figures 1-3).

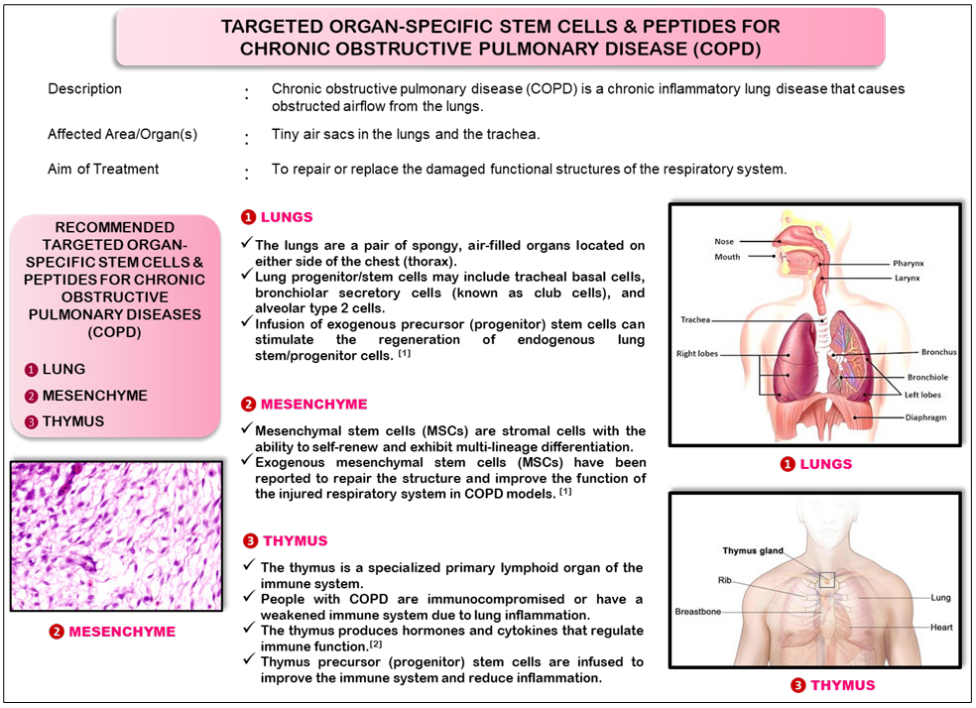

Figure 1: Recommended targeted organ-specific stem cells and peptides for Chronic Obstructive Pulmonary Diseases (COPD).

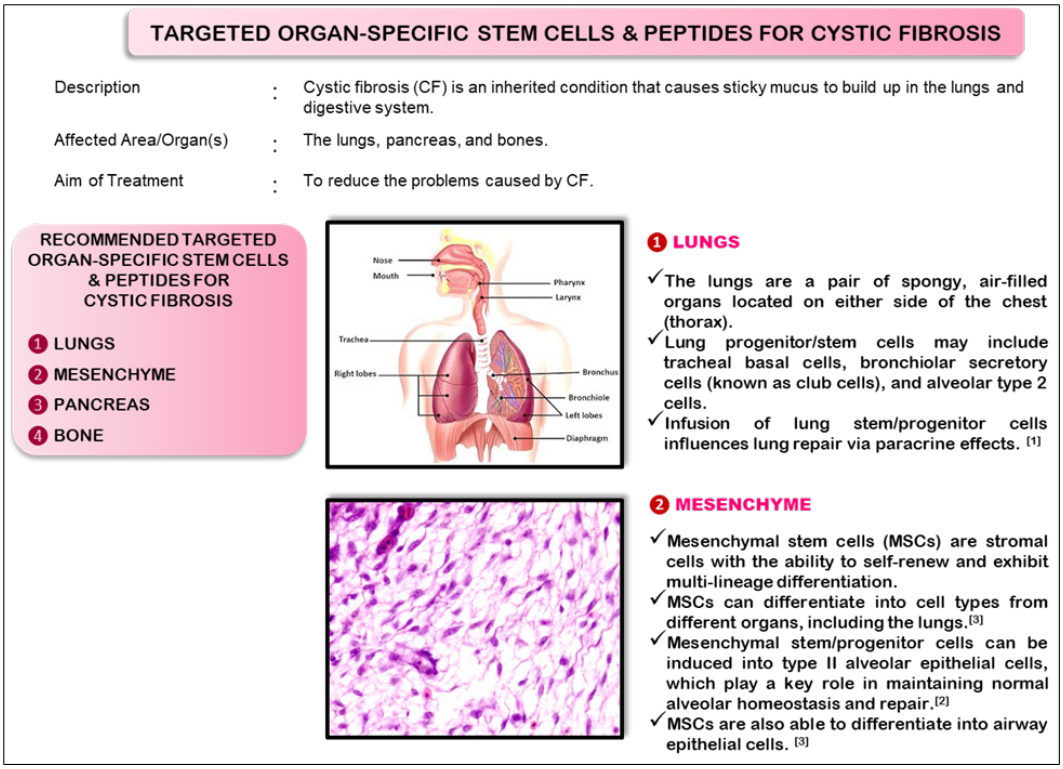

Figure 2: Recommended targeted organ-specific stem cells and peptides for Cystic Fibrosis (CF).

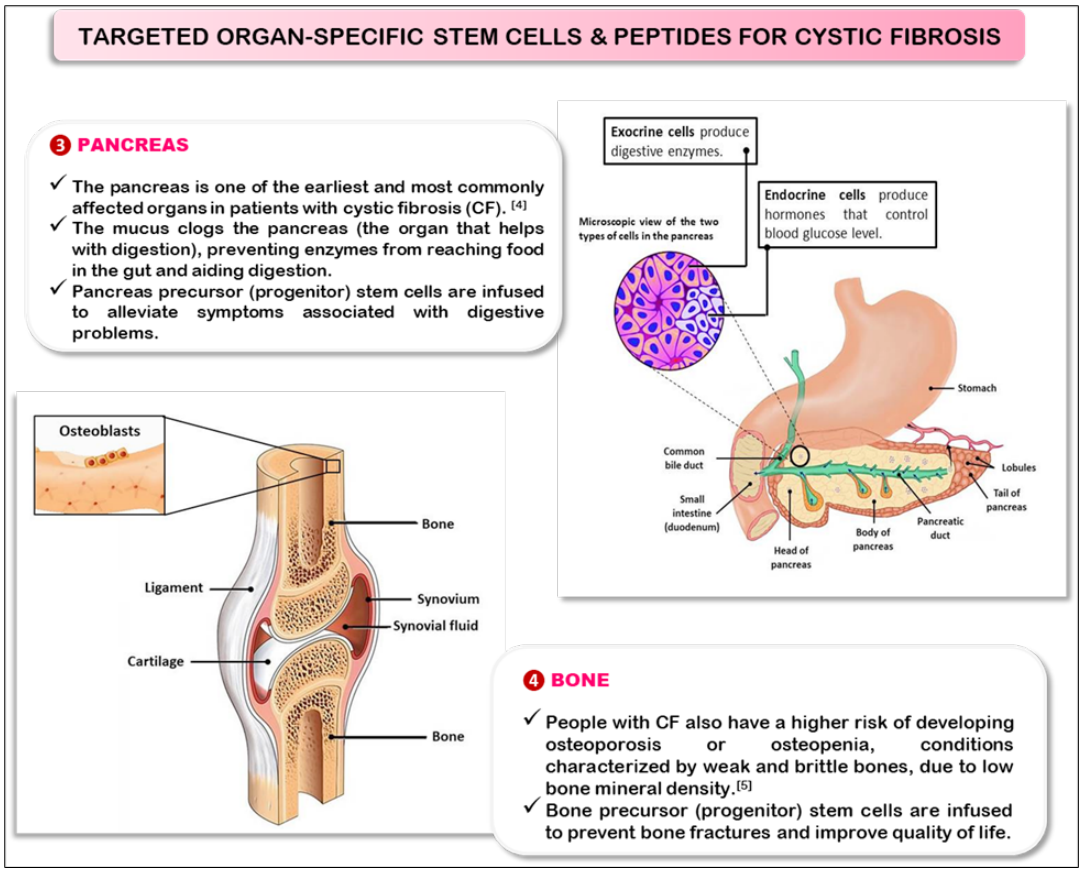

Figure 3: Recommended targeted organ-specific stem cells and peptides for Cystic Fibrosis (CF).

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Ethics Declaration

All authors declare that there are no ethical declarations to declare in relation to this manuscript.

Conflict of Interests

None.

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