

# Treatment of COPD: A matrix perspective

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**Abstract:** Fundamental physical properties, such as the intrinsic recoil of the lung, are governed by the extracellular matrix. The prototypical roles of the matrix proteins, collagen and elastin, in pulmonary fibrosis and emphysema have long been recognized, and much research effort has been devoted to understanding mechanisms of extracellular matrix synthesis and turnover in the lung. Yet, despite extensive knowledge of the biochemical properties of collagen and elastin, none of the present clinical strategies for treating COPD directly target the extracellular matrix. From a matrix perspective, therapeutic interventions that limit elastic fiber destruction and/or restore function to damaged alveolar units merit particular consideration as clinical strategies for treating the emphysema component of COPD. Effective treatment of the bronchiolar component of COPD requires a better understanding of the relationship between airway fibrosis and airflow obstruction. Translating basic knowledge of extracellular matrix biology into the clinical venue will be essential in the development of new approaches to COPD treatment.

**Keywords:** basement membrane, collagen, elastic fiber, emphysema, fibrosis, stem cell

## Introduction

The extracellular matrix is assembled into distinct three dimensional structures that play a key role in determining the physical and mechanical properties of an organ. In the lung, extracellular matrix organization is highly specialized to facilitate gas exchange. Lung extracellular matrix is partitioned into cartilage, provisional matrix, basement membrane, and interstitium. A brief discussion of the compartmentalization of lung extracellular matrix is found in the first part of this review. The extracellular matrix is composed of discrete gene products with specific functions. The basic biology of collagens and elastic fibers, matrix components that are fundamental to lung structure and function, is summarized in the next section. The review concludes with a description of COPD pathology that is associated with the extracellular matrix and a perspective on therapeutic strategies for COPD based on matrix-related pathology.

## Extracellular matrix compartments in the lung

### Cartilage

The walls of the trachea and large bronchi are lined by cartilage. Collagen fibers located in the outer layers of cartilage oppose tensile forces and proteoglycans in the central zone resist compression forces on the airways so that the changes in intrathoracic pressure that occur during breathing do not effect airway collapse (Roberts et al 1998).

### Provisional matrix

Provisional matrices are assembled during development or wound repair and are degraded when normal tissue architecture is achieved. The most common provisional matrix components are fibronectin and fibrin. Thrombospondin, tenascin, and SPARC may also form provisional matrix in the lung.

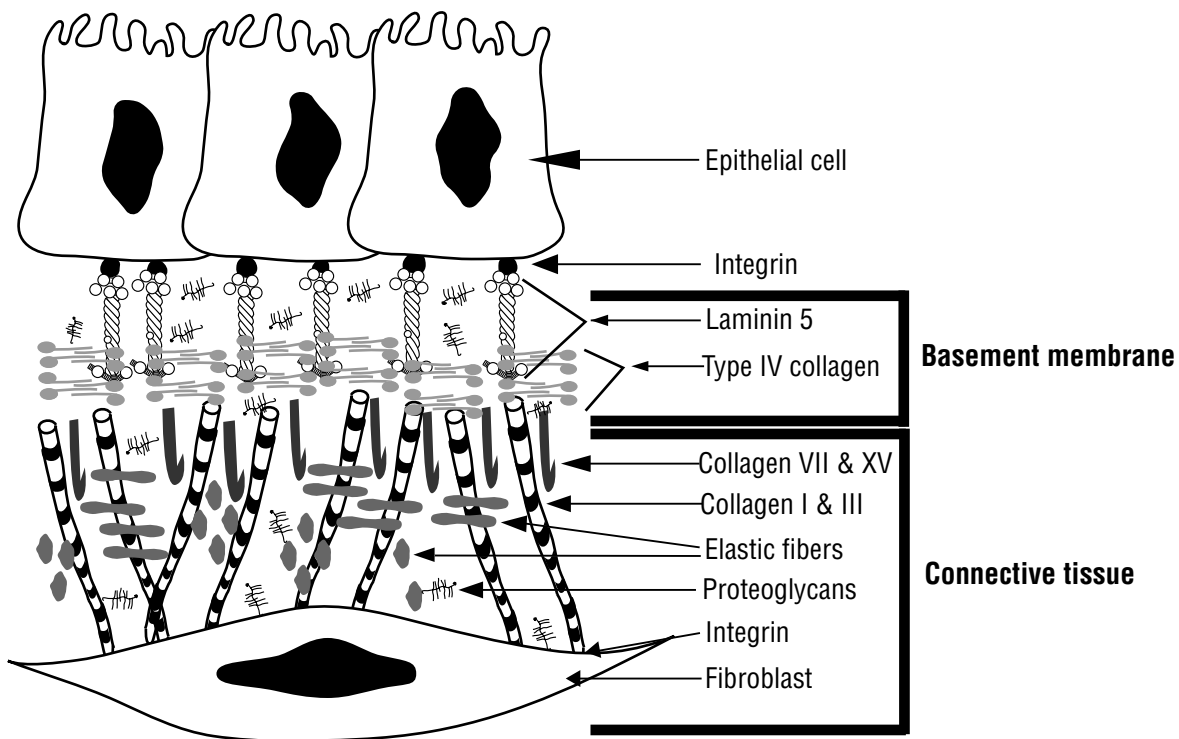
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## Basement membranes

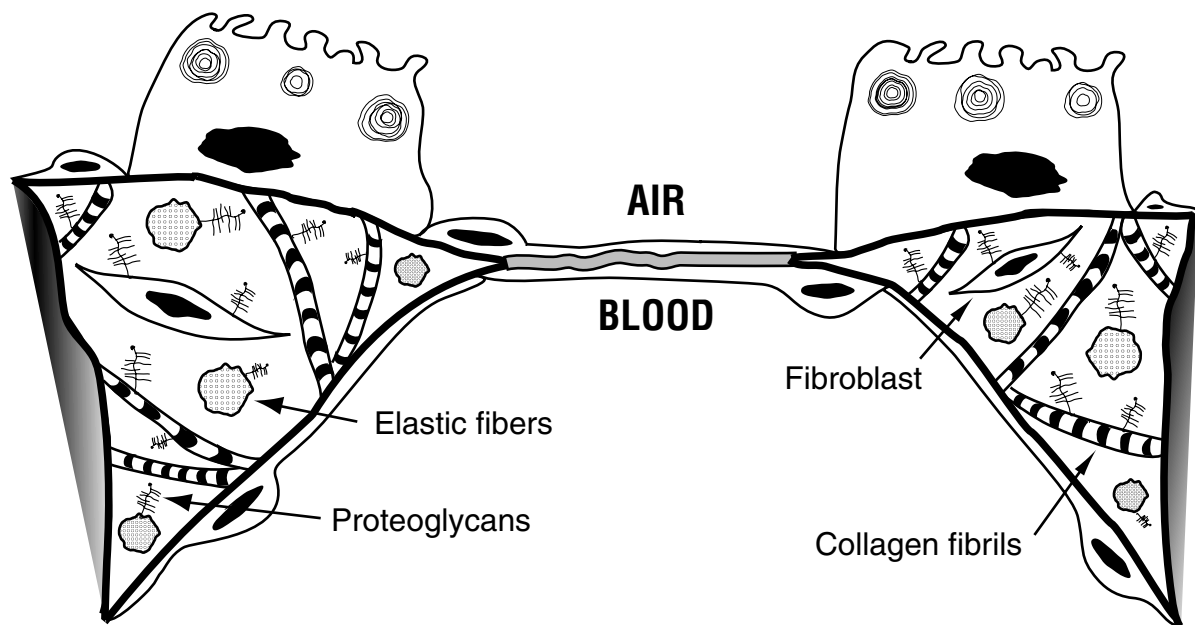
Basement membranes are found wherever parenchymal cells juxtapose connective tissue (Figure 1). Basement membranes provide physical support for an organ and also regulate macromolecular diffusion. In the lung, the type I alveolar epithelial and capillary endothelial basement membranes are fused thus providing a minimal barrier for gas diffusion. At the biochemical level, specific basement membrane components can modulate cell phenotype through direct interactions with cell surface receptors. Integrins are the best characterized cell surface receptors for matrix proteins and mediate both mechanical and chemical signals which activate a variety of intracellular signaling pathways to affect cell proliferation, survival, and differentiation (for review see Hynes 2002; Danen and Sonnenberg 2003; Hynes 2004). Airway branching and alveolar epithelial cell localization are influenced by the interactions of basement membrane components such as type IV collagen, laminin, fibronectin, and proteoglycans with cell surface receptors.

## The pulmonary interstitium

The pulmonary interstitium is located between the airspace epithelium and pleural mesothelium. Fibers of the matrix proteins, collagen and elastin, are the major components of the pulmonary interstitium. The primary function of these fibers is to form a mechanical scaffold that maintains structural integrity during ventilation (Figure 2). It has long been recognized that devastating pathology can result from disruption of pulmonary interstitial matrix homeostasis. Increased extracellular matrix synthesis and deposition, particularly of types I and III collagen, epitomizes pulmonary fibrosis. In fibrotic lungs, gas exchange is adversely affected by the obliteration of capillary beds and decreased regional compliance caused by the thickening of the pulmonary interstitium. Conversely, extracellular matrix degradation is a characteristic of pulmonary emphysema (Mandl et al 1977; Barnes 2004). In this disease, ventilation is negatively affected by the decreased intrinsic recoil of the lung that results from proteolytic destruction of elastic fibers (Christie 1934; Stead et al 1952; Mead et al 1955; Cherniack 1956).



**Figure 1** Basement membrane organization. Epithelial cells are linked to connective tissue via a network of matrix proteins. Laminin 5 connects integrins on the basal surface of epithelial cells to the type IV collagen network in the lamina densa of the basement membrane. Anchoring fibrils composed of type VII and type XV collagen link the basement membrane to the interstitial matrix where type I collagen, type III collagen and elastic fibers are found. Integrins located on the fibroblast cell surface interact with many matrix proteins including type I collagen. Copyright © 2003, 2007. Modified with permission from Dunsmore SE, Chambers RC, Laurent GJ. 2003. Matrix Proteins. Figure 2.1.2. In: Respiratory Medicine, 3rd ed. London. Saunders, p. 83; Dunsmore SE, Laurent GJ. 2007. Lung Connective Tissue. Figure 40.1. In: Chronic Obstructive Pulmonary Disease: A Practical Guide to Management, 1st ed. Oxford. Wiley-Blackwell, p. 467.



**Figure 2** Pulmonary interstitium. At the gas exchange interface alveolar capillaries and alveolar type I epithelial cells share a basement membrane. In other portions of the alveolar wall, collagen fibrils and elastic fibers are the major components of the pulmonary interstitium which also contains fibroblasts and proteoglycans. Copyright © 2003, 2007. Modified with permission from Dunsmore SE, Chambers RC, Laurent GJ. 2003. Matrix Proteins. Figure 2.1.1. In: *Respiratory Medicine*, 3rd ed. London. Saunders, p. 83; Dunsmore SE, Laurent GJ. 2007. Lung Connective Tissue. Figure 40.2. In: *Chronic Obstructive Pulmonary Disease: A Practical Guide to Management*, 1st ed. Oxford. Wiley-Blackwell, p. 468.

## Structural components of the pulmonary interstitium

### Collagens

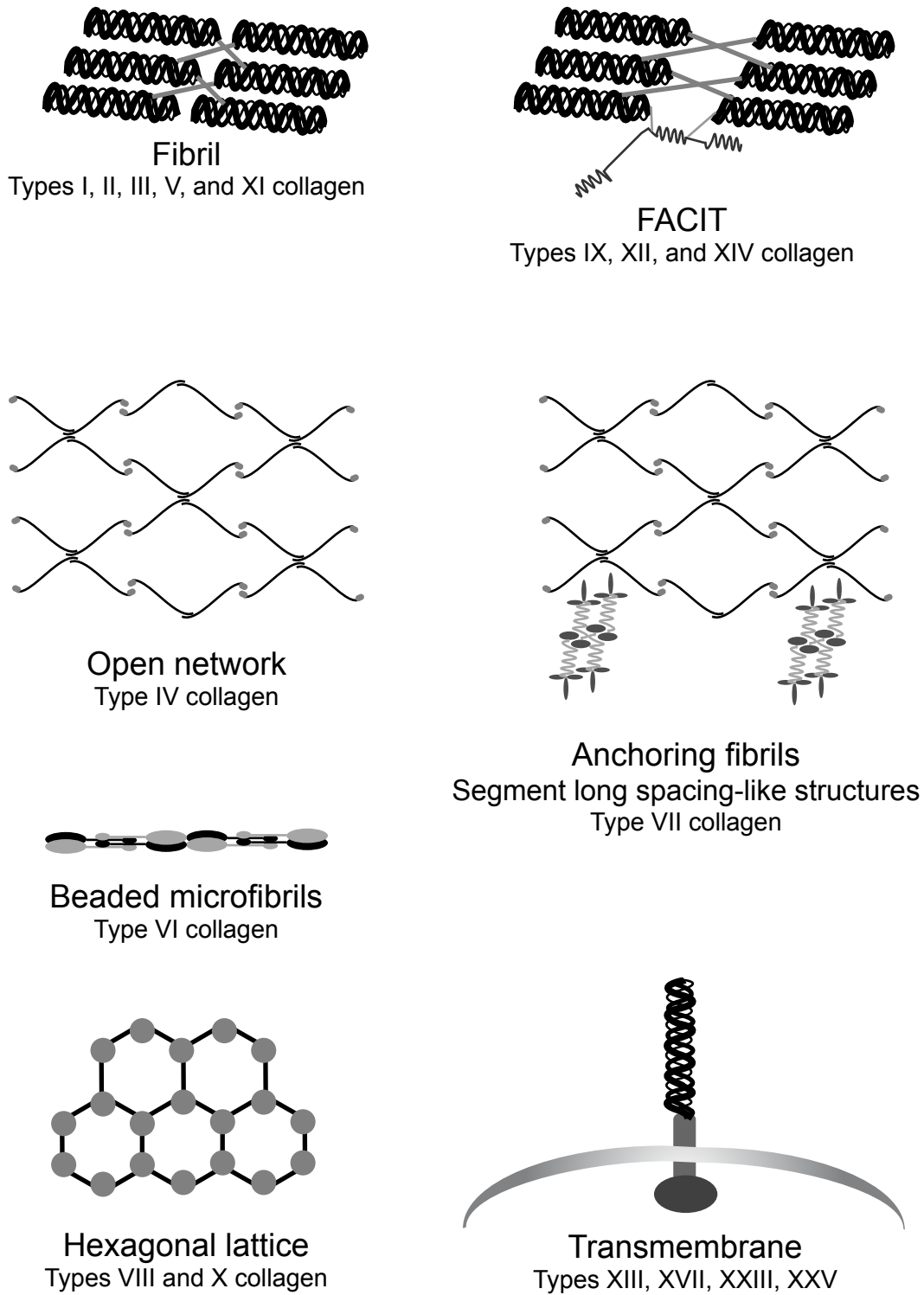
In simple terms, collagens may be thought of as the ‘struts’ of the lung; rod-like structures that limit lung deformation. The rod-like structures are composed of different types of collagen chains all of which contain a characteristic repeating sequence of three amino acids (Gly-x-y). Gly-x-y sequences associate to form triple helices, and by definition, all collagens contain at least one triple helical region (van der Rest and Garrone 1991). Collagen function is dependent on the formation of supramolecular structures from specific collagen polypeptide chains (Figure 3).

Fibrillar collagens (types I, II, III, V, and XI) are the most abundant proteins in the lung constituting approximately 15% to 20% of the dry weight of the tissue (Pierce and Hocott 1960). The primary function of fibrillar collagens is to provide tensile strength to all distensible components of the lung. Types I and III collagen perform this function in the alveolar interstitium, pulmonary blood vessels, visceral pleura, and connective tissue sheaths that surround the tracheobronchial tree. Types II and XI collagen are responsible for the tensile strength of bronchial and tracheal cartilage. Type IV collagen, the predominant component of basement membranes, is the most abundant

nonfibrillar collagen in the lung. The amino and carboxy terminal regions of the type IV collagen molecule laterally associate to form open-network structures that confer tensile strength to the blood-gas barrier and prevent stress failure of the pulmonary capillaries under normal conditions (West and Mathieu-Cosello 1999).

### Elastic fibers

Simplistically, elastic fibers are the springs that snap the lung back to resting volume following inflation. The primary component of elastic fibers (Kielty et al 2002), elastin (Mithieux and Weiss 2005), is composed mainly of hydrophobic amino acids (44%), glycine (33%), and proline (10%–13%). Two pentapeptides Val-Pro-Gly-Val-Gly and Pro-Gly-Val-Gly-Val repeat frequently in the molecule and are thought to form large spiral regions which contribute to the unique distensibility of the protein (Li and Daggett 2002). In the lung, elastic fibers are predominately found in the parenchyma where together with collagen fibrils, an integral fiber network which comprises the architectural skeleton of the lung is formed. Supramolecular assembly of elastic fibers in the lung is distinct. In the walls of the pulmonary artery and arterioles, elastic fibers are organized into concentric sheets or lamellae. Elastic fibers encircle respiratory bronchioles and alveolar ducts in a helical fashion and appear as a fine mesh in alveolar walls.



**Figure 3** Collagen supramolecular structures. Copyright © 2005. Modified with permission from Dunsmore SE. 2005. Extracellular Matrix: Collagens. Figure 2 In: Encyclopedia of Respiratory Medicine, 1st ed. London. Academic Press, p. 173; Dunsmore SE, Laurent GJ. 2007. Lung Connective Tissue. Figure 40.3. In: Chronic Obstructive Pulmonary Disease: A Practical Guide to Management, 1st ed. Oxford. Wiley-Blackwell, p. 470.

When appropriately assembled, elastic fibers will last for the entire life span of an organism (Shapiro et al 1991). Enzymatic cross-linking of tropoelastin lysine residues (Bedell-Hogan et al 1993; Thomassin et al 2005) and a transglutaminase cross-link between tropoelastin and fibrillin-1 (Rock et al 2004) are required for elastic fiber assembly (Figure 4). Other molecules such as fibulins (Nakamura et al 2002; Yanagisawa et al 2002; McLaughlin et al 2006) play important roles in tethering elastic fibers to cells during the assembly process. Elastic fibers cannot be repaired or replaced, thus irreversible pathology will result from elastin degradation. Recent evidence suggests that defects in elastic fiber assembly may enhance susceptibility to proteolysis (Kelleher et al 2005).

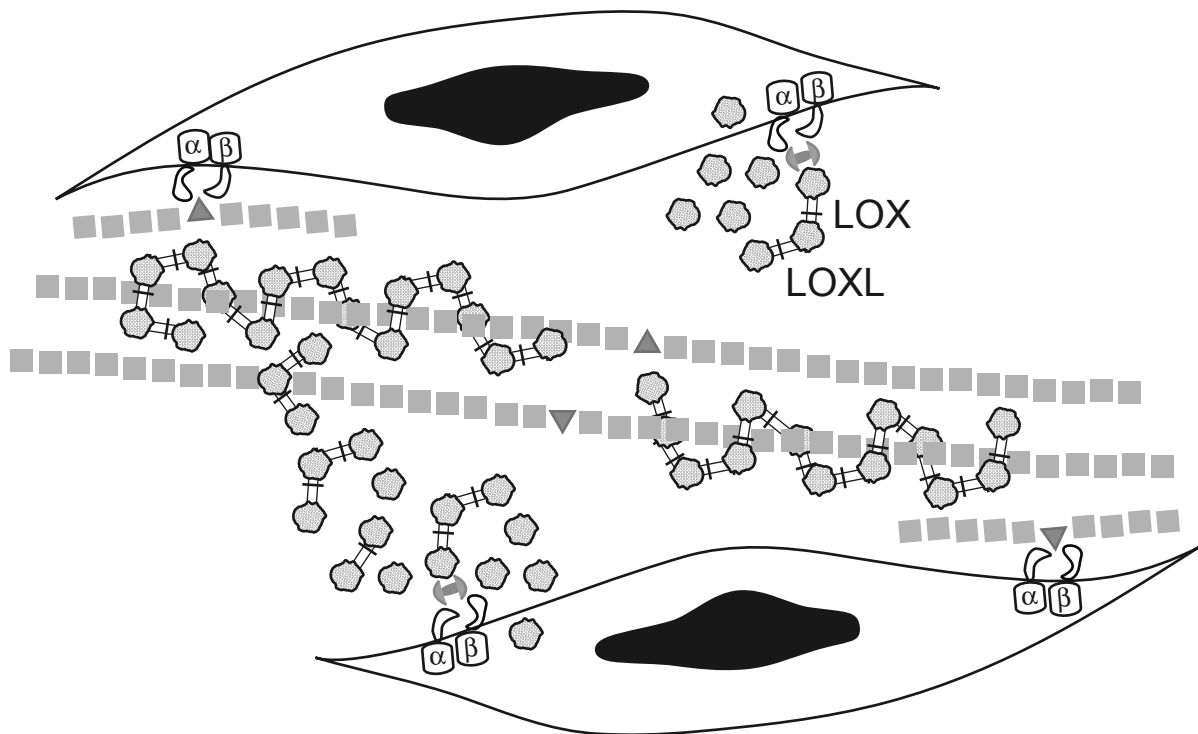
### Matrix-related pathology of COPD

Although the etiology of COPD can often be ascribed to a single factor ( $\alpha_1$ antitrypsin deficiency or exposure to cigarette smoke), the extracellular matrix-related pathology observed in COPD patients is rarely uniform. Airway fibrosis and emphysema are the most obvious pathological changes and are described in further detail below. Cartilage degeneration may accompany airway fibrosis in COPD

patients (Haraguchi et al 1999). Marked changes in the airway (Cosio et al 1980; Jeffery 2001) and alveolar epithelium (Otto-Verberne et al 1991) occur in COPD implying coexisting basement membrane aberrations. The compartmentalization and complexity of the lung extracellular matrix and the nonuniform nature of its response to the intrinsic and extrinsic factors associated with COPD should be taken into account when designing therapeutic strategies for COPD treatment.

### Airway fibrosis

Deposition of collagenous and noncollagenous matrix proteins in the airways is part of a larger remodeling process which also includes changes in airway smooth muscle and mucous glands. Historically, the ratio of mucous gland size to bronchial wall thickness (Reid 1960) was used to pathologically diagnose chronic bronchitis in the central airways (>4 mm in diameter). Thickening of the bronchial walls due to TGF- $\beta$  mediated collagen deposition is evident in the central airways of patients with chronic bronchitis (Vignola et al 1997), but the symptoms of chronic bronchitis do not appear to be predictive of the rapid decline in forced expiratory volume that occurs in COPD (Peto et al 1983; Vestbo and Lange 2002).



**Figure 4** Elastic fiber assembly. Fiber assembly begins on the surface of elastogenic cells where interactions with integrins are important for microassembly of tropoelastin and fibrillin. The enzymes, lysyl oxidase (LOX) and lysyl oxidase-like I (LOXL) begin to catalyze the oxidative deamination of lysine and hydroxylysine residues on the tropoelastin globules (●) that accumulate on the cell surface and continue the cross-linking process as the globules assemble on the microfibrillar scaffold (—) in the extracellular space.

Airway obstruction in the smaller conducting airways (<2 mm in diameter) does correlate with the overall severity of COPD (Hogg et al 2004). In severe disease (GOLD stage 3 and GOLD stage 4), thickness of all components of the small airway wall (epithelium, lamina propria, smooth muscle, adventitia) is increased (Hogg et al 2004). Fibrosis in the small airways is not well characterized. It is assumed that persistent inflammation in the small airways initiates a process of epithelial injury and repair and that fibrosis results from the subepithelial deposition of fibronectin and tenascin and the adventitial accumulation of collagen types I and III. Some modeling studies suggest that extracellular matrix deposition in the airways may be a teleological response to prevent airway collapse (Pare 1997). In COPD, however, the increased thickness of the walls of the small airways appears to directly lead to pathological narrowing of the airway lumen (Bosken et al 1990).

## Emphysema

Emphysema is typically classified as either panacinar or centrilobular. Panacinar emphysema predominates in the lower lung zones and results from  $\alpha_1$ -antitrypsin deficiency. Uniform destruction of the alveolar walls and permanent enlargement of the alveoli are observed. As the disease progresses, all respiratory airspaces distal to a terminal bronchiole are affected. Centrilobular emphysema predominates in the upper lung zones and begins with inflammation in the terminal and respiratory bronchioles with subsequent enlargement of the alveoli and more distal respiratory airspaces. Centrilobular emphysema is a consequence of prolonged exposure to cigarette smoke.

## Therapeutic strategies for COPD

Current COPD treatment regimens are designed to slow progression of the disease. Therapies may be behavioral (smoking cessation), pharmacological (bronchodilators, corticosteroids), replacement ( $\alpha_1$ -antitrypsin augmentation), or supportive (oxygen supplementation, pulmonary rehabilitation, nutritional support). In severe COPD cases, surgical intervention (lung volume reduction, transplant) may be an option. From a matrix perspective, therapeutic strategies that limit elastic fiber destruction and/or restore function to damaged alveolar units will most likely improve the clinical outcome of COPD. It is unclear if specific treatments for airway fibrosis, which remain to be developed, will prove to be beneficial in the COPD patient. Perspectives on protease inhibition, fibrosis reversal and alveolar regeneration in the context of COPD treatment ensue.

## Protease inhibition

Ever since the discovery of the association of  $\alpha_1$ -antitrypsin deficiency with emphysematous lung disease (Laurell and Ericksson 1963; Ericksson 1964), much effort has been focused on the design of neutrophil elastase inhibitors for COPD treatment. Indeed, the elastase-antielastase hypothesis has dominated the field of COPD research for the past 40 years. Many compounds designed to inhibit neutrophil elastase have been tested in animal models and in clinical trials (Ohbayashi 2002), but  $\alpha_1$ -antitrypsin remains the only neutrophil elastase inhibitor used in the routine clinical treatment of COPD. The design of therapeutic strategies based on antiproteases is complicated by the broad spectrum of extracellular and intracellular proteases, many with elastolytic capacity, that are present in the COPD patient (Shapiro 2001). Data from animal models (Hautamaki et al 1997; Zheng et al 2000) indicate that proteases other than neutrophil elastase may be important in elastic fiber destruction and COPD pathogenesis. Though it appears that the protease-antiprotease hypothesis may be more extensive than originally envisioned, effective inhibition of elastolytic proteases will continue to be an attractive strategy for attenuating COPD progression. Inhibition of nonelastolytic proteases may also be an effective strategy for limiting structural damage to the epithelium and basement membrane.

## Fibrosis reversal

Since bronchodilators do appear to alleviate some COPD symptoms (Weder and Donohue 2005), discussion of whether treatments that reverse airway fibrosis will be a stable and long-term means of preventing airflow obstruction may be warranted. Bronchial wall thickness and core-rind heterogeneity are the most predictive features of declining pulmonary function in COPD (Aziz et al 2005), but it is not known if modulation of bronchial wall thickness will correlate with improved pulmonary function in COPD. Data from computed tomography analyses may be used to develop prognostic algorithms for how changing bronchial wall thickness in an emphysematous lung affects pulmonary function. Animal models in which airway fibrosis can be uncoupled from emphysema in the presence and absence of inflammation are technically feasible and will be available for in vivo proof of concept testing of candidate molecules with fibrosis-reversing properties. Antifibrotic actions of potential therapeutics are likely to be cell type-specific, and potential antifibrotic agents as well as anti-inflammatory compounds already in clinical use should be tested in in vitro models in which the matrix-producing capacity of the structural cells of the airway wall



can be assessed. Recent evidence suggests that therapies that are equivalent in reducing inflammation may have dissimilar effects on fibrosis (Burgess et al 2006).

Several pharmacologics designed to inhibit or prevent fibrosis in the lung are in various stages of clinical development (Table 1). Most of these compounds have been designed to block the effects of cytokines on fibroblasts so that fibroblast proliferation and excess matrix production can be inhibited. Clinical trials testing the anti-fibrotic efficacy of drugs originally developed to treat other indications have also been conducted (Table 2). At the present time, however, the optimal pharmacotherapy for fibrosis reversal in any lung disease remains elusive.

Airway fibrosis in COPD is preceded by chronic bronchial inflammation. Thus, anti-inflammatory treatment if administered at the appropriate disease stage could potentially prevent the development of pathologic airway fibrosis in the COPD patient. Furthermore, many current anti-inflammatory therapies may have direct effects on the production of matrix proteins. For instance, glucocorticoids can inhibit the synthesis of collagen (Bavetta et al 1962; Shull and Cutroneo 1983; Oikarinen et al 1988). Phosphodiesterase 4 inhibitors block TGF- $\beta$  induced collagen production in airway smooth muscle cells (Burgess et al 2006). Animal model data suggest that corticosteroids (McMillan et al 2005; Cho et al 2005; Miller et al 2006) and antileukotrienes (Henderson et al 2006) may be effective at reversing airway fibrosis. Effects of anti-inflammatory therapeutics on airway fibrosis merit consideration as strategies for application of pharmacotherapy to COPD become more specifically adapted to disease stage and genetic background.

### Alveolar regeneration

To completely restore normal lung function to the COPD patient, repair and regeneration of damaged alveolar units is necessary. Clinical implementation of regenerative medicine remains a revolutionary and futuristic goal, but data from animal studies is providing evidence of some critical components of this process. The complexity of alveolar development is illustrated by the reports of defective alveogenesis in at least 11 distinct 'knock-out' mice (Mahadeva

and Shapiro 2002; Banerjee et al 2004; Chiang et al 2005; Mandeville et al 2006). Alveolar enlargement in mice deficient in surfactant protein D (Wert et al 2000), TIMP-3 (Leco et al 2001), or the  $\beta_6$  integrin subunit (Morris et al 2003) underscores the importance of these molecules in regulating alveolar homeostasis. Models in which emphysema is induced by apoptosis of alveolar endothelial (Kasahara 2000) or epithelial cells (Aoshiba et al 2003) highlight the role of parenchymal cell turnover in the maintenance of alveolar structure. Perhaps the most promising finding from animal studies is that in elastase-damaged lungs, alveolar function and architecture can be restored by retinoic acid treatment (Massaro and Massaro 1997). Translation of these findings in animal studies to clinical practice represents one of the most promising and challenging areas of COPD research.

In COPD, the capacity of the type II pneumocyte to proliferate and to restore the alveolar epithelium may be exhausted. Thus, alveolar regeneration might depend on the repopulation of damaged areas of the lung by stem cells. Recent progress indicates that "ethically acceptable" sources of human embryonic stem cells may be available for clinical use (Klimanskaya et al 2006). Understanding the pathways by which embryonic stem cells can be induced to differentiate into type II pneumocytes (Ali et al 2002), however, may provide sufficient information to develop either a pharmacological or biological means of stimulating proliferation of epithelial cells in emphysematous lungs.

Hematopoietic stem cells can also serve as progenitors for the alveolar epithelium (Krause et al 2001; Kotton et al 2001). Human pulmonary chimerism is observed following bone marrow transplant (Suratt et al 2003; Mattsson et al 2004; Albera et al 2005) and appears to be increased in the setting of chronic injury (Kleeberger et al 2003). Although it is likely that proliferation of type II pneumocytes is the predominant mechanism by which alveolar repair occurs (Zander et al 2005), hematopoietic stem cell engraftment may be particularly important for repair of areas of the lung in which emphysema has begun to develop. Clinical protocols for mobilizing hematopoietic stem cells are available should the engraftment of bone marrow-derived cells in the emphysematous lung prove beneficial.

**Table 1** Compounds in clinical development for treatment of fibrotic lung disease

Compound	Proposed mechanism	Status
BIBF 1120	Inhibits VEGF, PDGF and FGF receptors	Phase II clinical trial (NCT00514683)
FG 3019	CTGF neutralizing antibody	Phase I clinical trial (NCT00074698)
GC1008	TGF- $\beta$ neutralizing antibody	Phase I clinical trial (NCT00125385)
Pirfenidone	Inhibits collagen synthesis and fibroblast proliferation	Phase III clinical trials (NCT00287716, NCT00287729)

**Table 2** FDA-approved drugs tested for efficacy in treatment of fibrotic lung disease

Drug	Approved uses	Clinicaltrials.gov identifier of tests of efficacy in treatment of pulmonary fibrosis
Actimmune (Interferon Gamma-1b)	Chronic granulomatous disease Severe malignant osteopetrosis	NCT00047645 NCT00075998
Bosentan	Pulmonary arterial hypertension	NCT00071461 NCT00391443
Enbrel (Etanercept)	Rheumatoid arthritis Juvenile rheumatoid arthritis Psoriatic arthritis Ankylosing spondylitis	NCT00063869
Gleevec (Imatinib Mesylate)	Chronic myelogenous leukemia Gastrointestinal stromal tumor Dermatofibrosarcoma protuberans Philadelphia chromosome positive acute lymphoblastic leukemia Myelodysplastic syndrome Hypereosinophilic syndrome/chronic eosinophilic leukemia Aggressive systemic mastocytosis	NCT00131274

## Conclusions

Matrix-related pathology underlies many COPD symptoms. Treatments that restore lung function in COPD are needed. Knowledge of extracellular matrix biology can provide a basis for the development of new approaches to COPD treatment.

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