

## An Official American Thoracic Society Workshop Report: Comparative Pathobiology of Fibrosing Lung Disorders in Humans and Domestic Animals

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### Abstract

**Background:** The clinical outcome of idiopathic pulmonary fibrosis (IPF) is poor, with a 50% survival rate at 3 years. Furthermore, current treatments provide little amelioration of symptoms. Despite significant advances in understanding the clinical features and pathobiology of IPF, further advances have been hampered by a lack of suitable animal models of the disease. Interestingly, spontaneously occurring disorders with a similarity to IPF have been recognized in the dog, cat, horse, and donkey. These disorders share clinical and pathologic features with human IPF and are emerging diseases of veterinary importance.

**Purpose:** To improve awareness about these disorders in domestic animals and stimulate interactions between disciplines, and to facilitate the elucidation of mechanisms of fibrosing lung disorders using a comparative natural-occurrence disease model approach.

**Methods:** A 1-day meeting joined physicians, veterinarians, pathologists, researchers, and advocacy experts to discuss information available in this area. A review of the literature was conducted, and an executive committee discussed the findings and prepared a summary statement during subsequent meetings.

**Results:** Clinical, diagnostic, and treatment opportunities were identified, and common areas of interest where collaborative efforts could accelerate discovery regarding etiological factors, methods for early detection, determinants of disease progression, and novel therapies were defined.

**Conclusions:** Comparing fibrosing lung disorders in humans and domestic animals will allow for a better understanding of the similarities and differences among species and may offer novel insights into the underlying mechanisms of spontaneously occurring fibrotic lung diseases.

**Keywords:** lung fibrosis; comparative biology; domestic animals

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### Executive Summary

Idiopathic pulmonary fibrosis (IPF) continues to be an enigmatic disorder with poor outcomes and limited treatment

options. Interestingly, pulmonary disorders with similar clinical features are increasingly identified in animals such as dogs, cats, and horses, among others. Because they are long lived and share the same environment with humans, these animals might represent models of spontaneously occurring, progressive lung fibrosis. Learning about the pathogenesis of these conditions may provide novel insights that could be translated to the human condition and lead to the development of effective therapies in both humans and animals. To identify common areas of interest where collaborative efforts could accelerate

discovery about the etiology of these disorders, the factors that influence disease progression, and the development of effective therapies, a 1-day meeting sponsored by the Westie Foundation of America joined physicians, veterinarians, pathologists, researchers, and advocacy experts to discuss the information available in this area. Subsequently, a Working Group on Comparative Biology of Lung Fibrosis was established by the Respiratory Cell and Molecular Biology (RCMB) Assembly of the American Thoracic Society. Together with information gathered at the meeting, a review of the literature, and discussions

held through meetings and telephone conversations, the group came to the following conclusions:

- Although fibrotic lung disorders have been described for many years in horses, they have only more recently been described in other species, and there is little awareness of their occurrence in both the medical and veterinary communities.
- Significant advances have been made in the understanding of the clinical presentation, diagnostic methods, and treatment options in IPF; however, these advances have not led to safe and effective therapies capable of improving survival in this condition. Even less is known regarding pulmonary fibrosis in animals.
- Difficulties inherent in obtaining reliable information regarding the clinical presentation, physiology, imaging patterns of disease, and histopathology have greatly hampered progress in this area.

Considering the above, and to improve awareness and accelerate discovery that could lead to important advancements in this area, the group made the following research recommendations:

- Detailed descriptive studies should be conducted in affected domestic animals to define the clinical, imaging, and pathological presentation of pulmonary fibrosis in these species.
- Genetic studies and other pathogenesis-based investigations should be conducted in naturally occurring spontaneous models of pulmonary fibrosis to investigate the potential translation to IPF in humans. These models should provide more relevant tools to investigate the potential effectiveness of novel antifibrosis drugs in prehuman trials.
- Studies should be conducted to define the anatomical and cellular differences in the lungs of different species for the adequate interpretation of discordant findings.
- Suitable reagents needed to adequately test hypotheses in different species of animals should be generated.
- A consortium of interested centers and a central repository of clinical information and biologic specimens from naturally occurring spontaneous models of lung fibrosis in domestic animals should be established to enable further research that may benefit both physicians and veterinarians in their efforts to

adequately manage lung fibrosis in their patient populations.

- Another workshop including physician and veterinary experts, pathologists, community advocates, and representatives of private foundations, industry and biotechnology, and federal scientific organizations should be conducted to define specific hypotheses to be tested across species and the approaches to be used.

## Introduction

Idiopathic pulmonary fibrosis (IPF) is a pulmonary disorder characterized by progressive deposition of interstitial collagens and other extracellular matrix components in the lung, leading to fibrosis that invariably culminates in respiratory failure and death despite current therapeutic interventions, save for lung transplantation (1). The incidence of IPF is increasing in industrial nations, currently affecting more than 150,000 people in the United States alone, and more than 5,000 new cases are being identified annually in the United Kingdom, with many hundreds of thousands afflicted worldwide. Biomedical research into the molecular and genetic mechanisms of lung fibrosis has expanded our understanding of the processes that can lead to pulmonary fibrosis, but this work has not led to appreciable increases in the life expectancy of patients with IPF. Indeed, despite the considerable investment made to date, there are no Federal Drug Administration–approved drugs proven to prolong survival in patients with IPF (2, 3).

Central to the failure to make significant progress in understanding the pathogenesis of IPF and, by extension, to develop effective therapies and improve the clinical outcome in people with IPF, is the lack of an animal model that shares the progressive clinical course and pathologic features of the disease. The importance of this deficiency was highlighted in a 2002 summary of “Future Research Directions in IPF” released by a National Heart, Lung, and Blood Institute Working Group (4). More recently, Hunninghake and Schwarz suggested that data generated *in vitro* or in animal (i.e., rodent) models of lung fibrosis should not necessarily be assumed to translate to human IPF unless and until therapeutic intervention directed against such pathways or molecules is shown to ameliorate the clinical progression of the

disease or alter the histologic lung remodeling characteristic of IPF (5).

Unbeknownst to much of the medical community, spontaneous progressive fibrosing lung diseases are not restricted to human medicine; such diseases have been recognized for more than a decade in veterinary medicine in a variety of domestic animal species—most notably cats, dogs, and horses (6, 7). These disorders have received little attention in the biomedical community outside of veterinary medicine. Given that the affected species are long-lived animals that share a common environment with humans, they might represent potential models of spontaneously occurring, progressive lung fibrosis. Thus, it is conceivable that investigating fibrosing lung disease in these species could accelerate the development of effective strategies for the prevention and treatment of fibrosing lung disorders in both humans and domestic animals.

## Methods

To improve awareness and communication regarding spontaneous progressive fibrotic lung disorders in mammals and to stimulate interaction between human and veterinary medical professionals, the Westie Foundation of America (WFA) sponsored a 1-day meeting in October 2007 held in Lafayette, Indiana. The Westie Foundation of America, Inc. is a nonprofit corporation, recognized by the IRS as a 501 (C) (3) organization. Its mission is to provide financial aid and other support for medical research in order to benefit the health and quality of life of West Highland White Terriers; and to further develop and communicate information regarding the health, care, breeding, and quality of life of Westies to Westie owners, Westie breeders, and veterinarians. The aim of the WFA in organizing this symposium was to bring together a focused group of international physicians, veterinarians, pathologists, researchers, and advocacy experts to discuss fibrotic lung disorders in humans and domestic animals (*see* list of participants at the end of this article).

Leadership of the WFA, in communication with experts in the field, selected the participants for the symposium. Subsequently, a working group from this meeting was established by the American Thoracic Society’s (ATS) Respiratory Cell and Molecular Biology (RCMB) Assembly. Members of this working group

were selected from participants of the symposium, as well as members of the RCMB Lung Fibrosis Working Group interested in this topic, and were vetted for potential conflicts of interest according to the policies and procedures of the ATS.

This group met in May 2009 and 2010 in conjunction with the International ATS Conferences held in San Diego, California and New Orleans, Louisiana, respectively. The objectives of this working group were to extend the work performed at the Indiana meeting to identify new clinical, diagnostic, and treatment opportunities in IPF and related fibrotic lung disorders; to define common areas of interest where collaborative efforts could help accelerate the discovery of etiological factors, methods for early detection, determinants of disease progression, and novel therapies; and to generate recommendations that could serve to guide investigators and community advocates regarding investments in future research. Literature searches were conducted by several group members using both traditional biomedical and veterinary medicine search engines. Finally, a writing committee was established among the members of the working group and participants of the symposium to make research recommendations. Recommendations were formulated and differences were resolved by discussion and consensus (see Table 1).

**Workshop Discussion**

At the October 2007 meeting, physician experts in the area of IPF discussed the current state of knowledge regarding the idiopathic interstitial pneumonias (IIP) and described their clinical presentation, histology, and radiographic findings, using IPF as a prototype of IIP. In addition, researchers discussed processes related to epithelial cell injury, fibroblast differentiation and proliferation, matrix remodeling, surfactant protein mutations, viruses, and other potential etiologic factors and mechanisms implicated in the pathogenesis of IPF. Critical gaps in knowledge were discussed and the state of clinical trials was addressed. Further information about IPF can be found in recently published clinical practice guidelines from the American Thoracic Society, European Respiratory Society, Latin American Thoracic Society, and Japanese Respiratory Society (8).

Veterinary experts took the stage to discuss information available about spontaneous progressive fibrotic lung

**Table 1. Methodology**

Methods Checklist	Yes	No
Panel assembly		
Included experts from relevant clinical and nonclinical fields	x	
Included individuals who represented patients and society at large	x	
Included methodologist with appropriate expertise		NA*
Literature review		
Performed in collaboration with a librarian		X
Search multiple electronic databases	x	
Reviewed reference list of retrieved articles	x	
Evidence synthesis		
Applied preselected inclusion and exclusion criteria		X
Evaluated included articles for source bias		X
Explicitly summarized benefits and harms	x	
Used PRISMA1 to report systematic review		NA*
Used GRADE to describe quality evidence		NA*
Generation of recommendations		
Used GRADE to rate the strength of recommendations		NA*

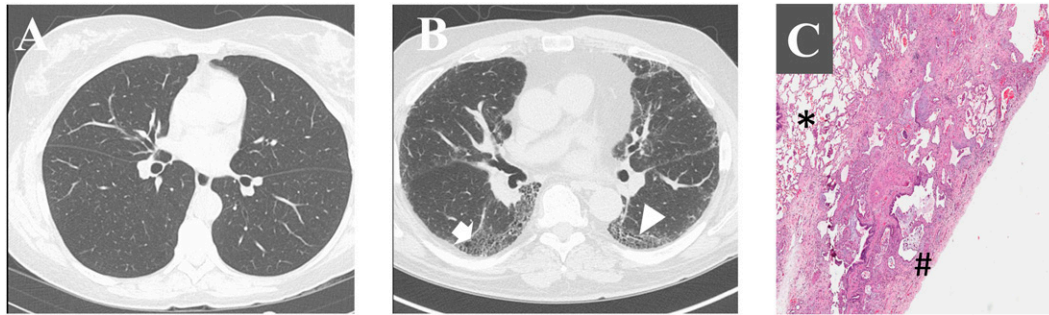
*Definition of abbreviations:* GRADE = Grades of Recommendation Assessment, Development, and Education; PRISMA1 = Preferred Reporting Items for Systematic Reviews and Meta-Analyses 1. \*Not required for workshop reports.

disorders in domestic animals. Although such diseases have been recognized for 20 years in horses, they have only more recently been described in dogs and cats (6, 7, 9–12). As in human medicine, the causes and factors associated with these disorders remain largely unknown. A gammaherpes virus, equine herpesvirus-5 (EHV-5), has been associated with a form of progressive lung fibrosis in adult horses. This finding may substantiate a role for gammaherpes viruses in lung fibrosis in humans, where Epstein-Barr virus is suggested to be a cofactor in the onset and/or progression of the disease (13).

In humans, the diagnosis of IPF and related fibrosing interstitial lung diseases depends on a well-characterized clinical-radiographic-pathologic presentation (Figure 1); such an approach is currently not developed in veterinary medicine because the necessary prospective clinical-radiographic-pathology studies have not been performed. In spite of this, veterinary medicine has borrowed terminology (i.e., IPF) from human medicine without having undergone the rigorous (and sometimes rancorous) debate and research that has occurred in human medicine. Naturally, this has led to some confusion when classifying these diseases in domestic animals. Regardless, it became apparent

throughout the meeting that the fibrosing lung diseases found in dogs, cats, and horses share several features in common with human IPF. For example, as in humans, the disease is diagnosed in middle-aged to old animals and is usually not detected until the disease is relatively advanced. Also, they are all progressive diseases that are largely poorly responsive to available therapies and usually lead to the death of the animal from respiratory failure. The prevalence of these disorders in each species is unknown. In cats and horses, there are no readily identifiable genetic (breed) predilections. In contrast, West Highland White Terriers, as well as other terrier breeds, develop fibrosing idiopathic interstitial lung disease more commonly than other breeds (10, 11, 14).

The pathophysiology of spontaneous progressive fibrosing lung disease in domestic animals is poorly characterized and has been evaluated in a limited way only in dogs (15, 16). These few studies highlight the need for standardized approaches to evaluate and follow the course of these lung diseases in domestic animals. Unfortunately, physiologic testing to evaluate restrictive lung disease, such as FVC, is difficult to perform in nonhuman animals due to difficulties with patient cooperation. Thoracic imaging, especially high-resolution computed tomography, has



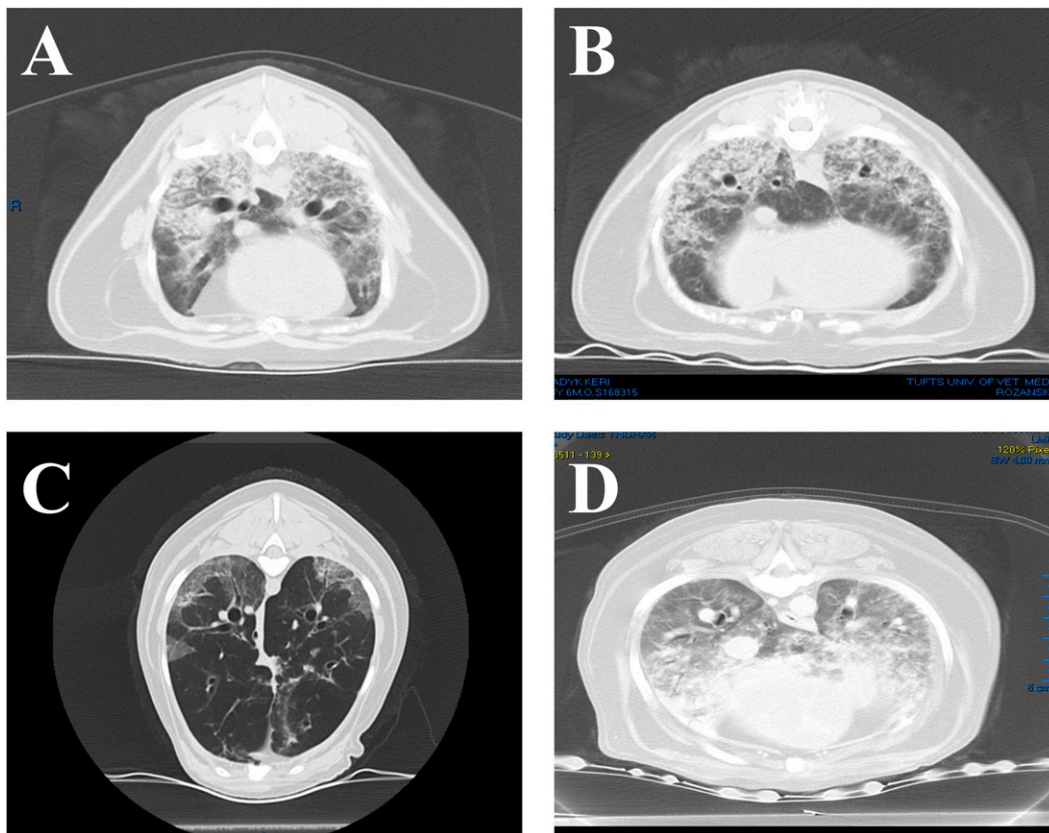
**Figure 1.** Computed tomography (CT) image and histology of idiopathic pulmonary fibrosis (IPF). (A) CT image of normal human lung. (B) CT image of subject with IPF. Note infiltrates predominating in the lower lobes posteriorly with evidence of honeycombing (*arrow*) and traction bronchiectasis (*arrowhead*) with absence of pleural abnormalities. (C) Tissue section of lung obtained from subject with IPF. Note normal alveolar spaces (*star*) adjacent to fibrotic tissue and areas of honeycombing (*#*).

been performed in cats and dogs with suspected diffuse parenchymal lung disease (Figure 2) and in rodents, but detailed prospective studies are lacking in any nonhuman species (17). In dogs, ground-glass opacification and traction bronchiectasis have been identified (Figure 3).

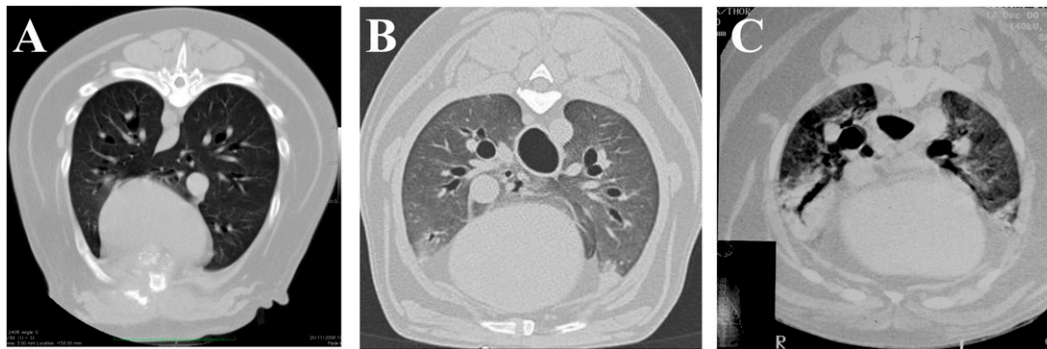
Similar needs for prospective investigations were identified regarding the histologic characterization of these

disorders in nonhuman animals. Important correlates with the usual interstitial pneumonia (UIP) histologic pattern, the characteristic pattern observed in human IPF, have been reported in domestic animals. Such important correlates include subpleural involvement, minimal cellular inflammation, the presence of myofibroblasts, temporal heterogeneity of fibrosis with evidence of ongoing

fibroproliferation, regions reminiscent of “fibroblast foci,” and the formation of “honeycomb” lung (12) (Figure 4). Unfortunately, the establishment of clear histologic criteria to facilitate distinguishing differing patterns of interstitial lung disease and correlating them with the clinical presentation and outcomes, (a critical advance in our understanding of human IIP [18]), are missing in nonhuman mammals.



**Figure 2.** Chest computed tomography (CT) imaging of animals. (A, B) Chest CT image in cat with lung fibrosis. (C, D) CT image in dog with lung fibrosis.



**Figure 3.** Chest computed tomography (CT) imaging in canine lung fibrosis. (A) Normal CT image. (B) CT image showing ground-glass opacification. (C) Severe fibrosis with traction bronchiectasis.

The progressive nature of these diseases in domestic animals and their lack of response to therapeutic intervention are important features that are not present in conventional experimental animal models of pulmonary fibrosis. At the meeting, significant emphasis was put on the limitations of our current treatment strategies and the lack of progress in this area in both IPF and lung fibrosis in animals. Corticosteroids, which have been often used for the treatment of IPF despite the lack of supporting data, are also often tried in animals, with variable and generally limited success. Formal trials in domestic animals have not been conducted with this or any other agents recently tested in IPF.

### Research Recommendations

Considering the above, the group generated research recommendations that we hope will help guide investigators interested in using comparative biology to accelerate meaningful discoveries in this field. These recommendations can be summarized as follows:

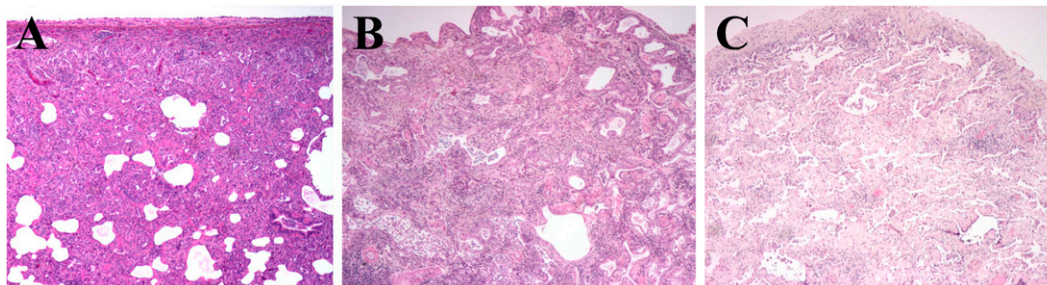
- Detailed descriptive studies should be conducted in affected domestic animals to define the clinical, imaging, and pathological presentation of pulmonary fibrosis in these species.
- Genetic studies and other pathogenesis-based investigations should be conducted in naturally occurring spontaneous models of pulmonary fibrosis to investigate the potential translation to IPF in humans. These models should provide more relevant tools to investigate the potential effectiveness of novel antifibrosis drugs in prehuman trials.
- Studies should be conducted to define the anatomical and cellular differences in the lungs of different species for the adequate interpretation of discordant findings.
- Suitable reagents needed to adequately test hypotheses in different species of animals should be generated.
- A consortium of interested centers and a central repository of clinical information and biologic specimens from naturally occurring spontaneous models of lung fibrosis in domestic animals should be established to enable further research that may benefit both physicians

and veterinarians in their efforts to adequately manage lung fibrosis in their patient populations.

- Another workshop including physician and veterinary experts, pathologists, community advocates, and representatives of private foundations, industry and biotechnology, and federal scientific organizations should be conducted to define specific hypotheses to be tested across species and the approaches to be used.

### Summary

Comparative medicine is a well-established discipline in which diseases encountered in nonhuman animals offer powerful clues for understanding diseases that also affect humans (19). It is our hope that by taking such an approach, and by implementing the above recommendations, we will advance our understanding of IPF, lung fibrosis, and lung disorders in general. The sequencing of many of the companion animal genomes and the significant conservation of the genome among mammals should allow



**Figure 4.** Histology of lung fibrosis in animals on *post mortem* examination. (A) Equine pulmonary fibrosis. Note nodular interstitial and alveolar inflammation. (B) Feline pulmonary fibrosis showing subpleural localization, temporal heterogeneity, and honeycomb lung formation. (C) Canine pulmonary fibrosis developing subpleurally but lacking obvious temporal heterogeneity. Honeycomb lung formation not present.

investigators to go beyond clinical observations within this field and support findings with genetic and molecular data. By examining the natural progression of these spontaneous diseases in animals, our understanding of complex diseases and the development of therapeutic interventions is likely to be accelerated (20). It is expected that collaborative efforts between human and veterinary clinicians and researchers will ultimately provide new insights and advance scientific knowledge in ways that will allow for the prevention, treatment and improved outcome in fibrotic lung disorders in humans and domestic animals. ■

This official statement was prepared by an *ad hoc* subcommittee of the ATS Assembly on Respiratory Cell and Molecular Biology.

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