



# Research in Pulmonary Fibrosis Across Species: Unleashing Discovery Through Comparative Biology



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**P**rogressive scarring of the lung, also termed pulmonary fibrosis, has become the focus of many basic, translational and clinical investigations throughout the world. To date, this research has revealed much needed information about the epidemiology and pathogenesis of pulmonary fibrosing disorders, with particular attention to idiopathic pulmonary fibrosis (IPF), the most common of the idiopathic interstitial pneumonias and the most devastating due to its poor prognosis.<sup>1</sup> However, despite many recent advances, only 2 so-called antifibrotic drugs are currently approved for the treatment of IPF; these drugs slow-down lung function decline, but do not improve the condition, and their role in other progressive fibrosing lung disorders remains unknown.<sup>2</sup> Thus, much research is still needed to gain further insights into the pathogenesis of these disorders, to identify reliable diagnostic and prognostic biomarkers, and to develop effective and safe interventions that improve survival. If successful, this research has the potential of positively affecting the natural course of related fibrosing disorders of the skin, kidney, heart, liver and other organs.

A major hindrance to progress in pulmonary fibrosis research is the lack of animal models capable of better resembling fibrosing lung disorders in humans and adequately predicting the efficacy of new interventions. Most animal models of pulmonary fibrosis available today require induction of lung injury by exogenous agents (e.g., bleomycin) and do not adequately model human disease, thereby raising questions about their

utility in the quest for novel treatments.<sup>3</sup> Even if animal models were able to duplicate most of the characteristics of human disease, such as the usual interstitial pneumonia or UIP histologic pattern found in IPF, it would be difficult to duplicate the genetic and environmental factors that contribute to disease development in humans. This, compounded by the anatomic and behavior differences between animals and humans, has prevented the development of a truly relevant model.<sup>4</sup>

Interestingly, spontaneous progressive pulmonary fibrosis is not restricted to humans. In fact, this disorder has been recognized for over 2 decades in veterinary medicine in a variety of domestic animal species including cats, dogs and horses.<sup>5,6</sup> Unfortunately, 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 relevant models of spontaneously occurring, progressive lung fibrosis. If so, investigating pulmonary fibrosis in these species could advance progress in this area.

Because of the potential of such approaches to accelerate discovery and to promote awareness, communication and collaboration regarding spontaneous progressive fibrosing lung disorders in mammals, the Westie Foundation of America (WFA) sponsored a 1-day meeting in October 2007 held in Lafayette, Indiana, USA. The WFA is the official breed association of the West Highland Terrier, a breed of dogs that is known to be afflicted with progressive lung fibrosis. This workshop

brought together international physicians, veterinarians, pathologists, researchers and advocacy experts to discuss fibrotic lung disorders in humans and domestic animals. Afterward, a working group of the American Thoracic Society and participants of the initial workshop reported on the workshop findings and made the following recommendations<sup>7</sup>: (1) Promote the conduction of detailed descriptive studies in affected domestic animals to define the clinical, imaging and pathologic presentation of pulmonary fibrosis in these species; (2) Emphasize the need for performing genetic studies and other pathogenesis-based investigations in naturally-occurring spontaneous models of pulmonary fibrosis to investigate the potential translation to IPF in humans as these models should provide more relevant tools to investigate the potential effectiveness of novel antifibrosis drugs in prehuman trials; (3) Emphasize the need for studies defining the anatomic and cellular differences in the lungs of different species for the adequate interpretation of discordant findings; (4) Stimulate the generation of suitable reagents to adequately test hypotheses in different species of animals; and (5) Promote the establishment of 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 to enable further research that may benefit both physicians and veterinarians in their efforts to adequately manage lung fibrosis in their patient populations.

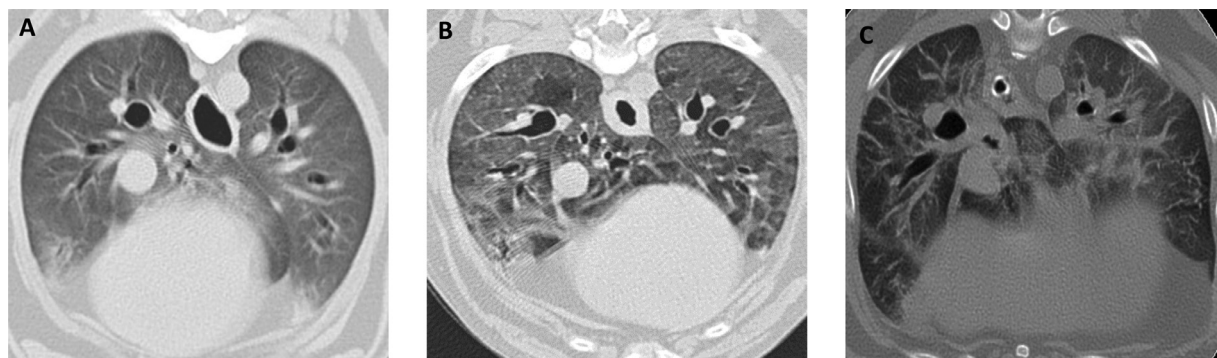
In May 2014, a second meeting on Comparative Biology of Pulmonary Fibrosis was held in Louisville, Kentucky. As before, clinicians, researchers, veterinary doctors, pathologists and patient advocates came together to discuss the state of research in this field. The meeting was again endorsed by members of the Working Group on Lung Fibrosis of the Assembly of Respiratory Cell and Molecular Biology of the American Thoracic Society, and was supported by industry, The Westie Foundation, The Morris Animal Foundation and The AKC Canine Health Foundation. During the meeting, extensive

discussions surrounded the limited progress made in the field since the first meeting. However, energized by the potential this field of investigation could have on understanding fibrosing lung disorders, the team powered through an ambitious agenda hoping to define a new path for such efforts. The proceedings of this meeting were not published; however, considering the perceived importance of the discussions held, a group of meeting organizers and participants came together to summarize its proceedings in this document.

The group discussion first focused on the fact that key clinical manifestations of pulmonary fibrosis are common in both humans and domestic animals. These similarities are best highlighted in recent publications showing that in canine IPF, for example, the disease is a chronic, progressive, interstitial lung disease affecting mainly middle-aged and old West Highland white terriers.<sup>8</sup> It is clinically characterized by exercise intolerance, restrictive dyspnea and coughing, and course crackles are present on lung auscultation. Abnormal blood gases and shortened "6-minute walk test" distance, a test that evaluates endurance and gas exchange capability, are common, and secondary pulmonary hypertension is not infrequent.<sup>9</sup> These data emphasize the striking similarities in the clinical presentation of spontaneously occurring pulmonary fibrosis observed in humans and domestic animals as highlighted previously.<sup>7</sup>

More data about the imaging presentation of pulmonary fibrosis in domestic animals have also emerged (see [Figure 1](#)). In a retrospective study including 21 West Highland white terriers (WHWT), the severity of pulmonary computer tomography (CT) findings was positively correlated with severity of clinical signs, and negatively associated with survival time after diagnosis. The most common CT findings included ground glass pattern (16/21 dogs) and focal reticular and mosaic ground-glass opacities (10/21 dogs), with very rare and minimal honeycombing identified.<sup>10</sup>

In addition to the above, the group also discussed that noted similarities between dogs and humans began



**FIGURE 1.** Computed tomography scan image of dog with pulmonary fibrosis. (A) Ground glass opacity in mildly affected dog. (B) Extensive ground glass opacity with prominent mosaic attenuation in moderately affected dog. (C) Ground glass opacity, traction bronchiectasis and parenchymal bands in severely affected dog.

to dissipate when evaluating the pulmonary histopathologic findings present in these conditions. In 18 WHWT with canine IPF, a pattern resembling NSIP was predominant rather than a pattern of UIP.<sup>11</sup> NSIP, for nonspecific interstitial pneumonia, is another histologic pattern observed in another type of idiopathic interstitial pneumonia. In contrast to UIP, the NSIP pattern is more homogenous throughout the lung, shows more cellularity and less fibrosis, and fibroblastic foci are not typical; this entity is considered responsive to immunosuppression in many circumstances in humans.<sup>12</sup> The majority of the dogs tested showed multifocal areas of accentuated subpleural and peribronchiolar fibrosis with what was reported as occasional honeycombing and “profound” alveolar epithelial changes, and fibroblastic foci were not seen. In some cases, intra-alveolar organizing fibrosis adjacent to interstitial mature collagen deposition was observed, especially in more severely affected areas. Interestingly, severe pulmonary lesions were more frequent in the caudal than in the cranial lung lobes. The increased availability of high-resolution computed tomography data from affected dogs, coupled with the limited pathologic data already available, support the contention that the canine form of IPF is in fact NSIP. Case cohort studies are now ongoing at the University of Edinburgh Veterinary School to assess the clinical response of affected dogs to immuno-suppressive therapy with prednisolone and mycophenolate to determine if this indeed behaves as NSIP. Furthermore, while the ground glass attenuation and mosaic pattern on HRTC can be associated with hypersensitivity pneumonitis, this condition can be excluded as it is not recognized in the dog. One confounding factor, however, is the often-late presentation of affected dogs with extensive fibrosis making measurable response to trial therapy problematic.

In evaluating 9 cats carrying a diagnosis of pulmonary fibrosis based on radiographic findings, investigators found focally increased soft tissue attenuation, masses and ventral consolidations that exhibited no improvement with dorsal vs. ventral recumbence.<sup>13</sup> On histology, pulmonary fibrosis in these cats was evident with type II pneumocyte hyperplasia and smooth muscle hypertrophy. Epithelial metaplasia was present in one case. However, they also observed changes consistent with a broncho-interstitial pattern, alveolar pattern, pulmonary masses, pulmonary bullae, pleural effusions and cardiomegaly. Overall, the findings suggested highly variable radiographic characteristics, which might mimic pulmonary fibrosis, but also other conditions such as asthma, pneumonia, pulmonary edema and neoplasia.

In another study, 23 cats with a histology of UIP were investigated.<sup>14</sup> Most were middle-aged to older cats (median 8.7 years) with no obvious sex or breed predisposition. Symptoms included respiratory distress and cough. Duration of signs was less than 6 months in 17 cats. Exam revealed tachypnea, inspiratory or mixed

inspiratory and expiratory effort, and adventitial lung sounds. Radiographic changes included dense patchy or diffuse interstitial, bronchiolar, and alveolar infiltrates. BALF revealed mild neutrophilic inflammation in 6 cases, with no consistent pathogen identified. Response to steroids is poor and most cats died within days to months.

Horses also develop pulmonary fibrosis, known as equine multinodular pulmonary fibrosis or EMPF because of its characteristic imaging and histologic patterns that are distinct from UIP in the setting of IPF in humans. Emerging data point to the equine gamma Herpes Virus 5 as the cause of EMPF as investigators have been able to experimentally reproduce EMPF in horses inoculated with EHV 5 isolated from cases of EMPF.<sup>15,16</sup>

Overall, the group remained impressed with the similarities observed in symptoms, lung examination, abnormalities in oxygenation and imaging studies, and outcomes when comparing humans and domestic animals with pulmonary fibrosis. However, the differences observed in histopathology strongly argue against these being identical conditions. This prompted discussions regarding mechanisms of action and several presentations were devoted to this topic. To date, there is consensus that IPF and other forms of fibrosing lung disease are likely triggered by certain exposures in the setting of host genetics that render the lung epithelium susceptible to injury. In turn, epithelial cell injury leads to its dysfunction and the subsequent elicitation of intracellular pathways responsible for the overexpression of soluble profibrotic growth factors. Of these, transforming growth factor- $\beta$  (TGF $\beta$ ) is considered the most influential, but many other activated signals exert pro-fibrotic activity. The above results in the proliferation of fibroblasts and the excessive expression and deposition of fibronectin, collagens, and other extracellular matrices that ultimately destroy the delicate architecture of the lung and its gas-exchanging units.<sup>17</sup> New data regarding the potential role of oxidative stress, dysregulated miRNAs, epigenetics, telomere shortening, tissue stiffness, aberrant metabolism, altered immunity, and aging have further added depth to our understanding of mechanisms of disease, but it is too early to determine if this new knowledge will lead to clinical tools capable of affecting patient outcomes.<sup>18</sup>

Similar mechanisms are likely present in canine IPF as TGF $\beta$  protein was detected by immunohistochemistry in areas of fibrosis, and a receptor for TGF $\beta$ , TGF $\beta$ RI and a transcription factor known for promoting its intracellular effects, pSMAD2/3, were found in the epithelium.<sup>19</sup> Interestingly, latent binding TGF $\beta$  protein gene expression was decreased as was  $\beta$ 8 integrin; these changes have been proposed to ultimately affect TGF $\beta$  activation. Another extracellular matrix implicated in pulmonary fibrosis, thrombospondin-1, also appeared upregulated. Of note, circulating TGF $\beta$ 1 concentrations in the periphery were higher in animals “predisposed” to pulmonary fibrosis compared to “nonpredisposed”

breeds.<sup>20</sup> Alveolar interstitial fibrillin-2 immunoreactivity was upregulated in WHWTs as well. This is similar to what has been found in the idiopathic interstitial pneumonias in humans.

Chemokines have also been implicated in the pathogenesis of IPF. Similarly, higher levels of CCL2 and CXCL8 have been detected in bronchoalveolar lavage fluid obtained from affected WHWTs compared to healthy dogs.<sup>21</sup> Circulating levels of CCL2, but not CXCL8, were reported in the same animals. In contrast, no differences in relative gene expression for CCL2, CXCL8, CCR2 or CXCR2 were observed when comparing the lung biopsies of control vs. affected animals. In those affected, CCL2 and CXCL8 immunoreactivity was detected in bronchial airway epithelial cells. In other work, Activin B, a cytokine member of the TGF $\beta$  superfamily, was found to be upregulated in the bronchoalveolar lavage fluid of WHWTs with canine IPF, but not Activin A.<sup>22</sup> These studies suggest that similar mechanisms of action are acting in both human and animal forms of spontaneous pulmonary fibrosis, but they fail to explain how such pathways lead to distinct histologic patterns observed between species.

## CONCLUSIONS, CHALLENGES AND RECOMMENDATIONS

Overall, the discussions of the 2014 meeting emphasized a concept unveiled during the earlier meeting. Namely, that domestic animals develop spontaneously occurring interstitial lung diseases that can result in pulmonary fibrosis and share features with the human condition. While prior discussions centered on the possibility that some of these animals may develop disease identical to the human condition, the more recent histopathologic studies available suggest that domestic animals develop diseases with clinical manifestations similar to those of human IPF, but are likely distinct from that condition. Nevertheless, the group felt that, while identifying a model identical to the human condition would be preferable, a more realistic goal would be to simply identify better models of spontaneously occurring disease than those currently used today; domestic animals such as the WHWT might provide such a model.

Two important challenges hindering progress in this area remain present today. The first relates to difficulties inherent in communicating about these disorders considering that domestic animals with pulmonary fibrosis are simply referred to as having IPF (e.g., canine IPF), which is confusing as these animals do not appear to adequately mimic human IPF. The group recommends that the term "*idiopathic interstitial pneumonia or IIP*" be used as this reflects classifications used in human disease. For example, instead of canine IPF, the term canine IIP should be used, at least until these IIPs are better defined.

The above challenge is directly linked to gaps in disease definition due to an inadequate understanding

of the clinical, histologic and radiographic manifestations of pulmonary fibrosis in distinct animal species. Greater understanding of IPF and related idiopathic interstitial pneumonias in humans came after defining their distinct clinical, radiographic, and histologic presentations. In fact, today, an accurate diagnosis of these human conditions remains dependent on the interpretation of the aggregate clinical, radiographic and histologic data. This knowledge laid the foundation for the emergence of standardized, placebo-controlled, and randomized clinical trials that culminated in the identification of anti-fibrotic drugs. Unfortunately, this information is not available for domestic animals. To date, studies correlating the clinical, radiographic and histologic presentations of domestic animals with fibrosing lung disease are very limited, and a clear classification of these disorders and diagnostic algorithms remain to be developed. Success in collecting such data would be greatly accelerated by the establishment of domestic animal clinical registries well linked to tissue and other biological sample repositories. Such repositories may be located at specialized veterinary centers with interest and expertise in this field. Undoubtedly, the resources needed to support such endeavor are significant and may originate in industry, private foundations and government agencies.

In short, domestic animals develop spontaneously occurring fibrosing lung disease that resembles the human condition. Although not identical, these models might be superior to those used today when testing mechanisms of action and the effectiveness of novel interventions. However, this will first require a better classification of fibrosing lung disorders in domestic animals based on clinical, radiographic and histologic presentations. Obtaining the information needed to develop such classification would benefit from a registry of clinical data and biological samples. The molecular tools needed to test genetic variants and mechanisms of action and to unveil potential targets for intervention are available, but this will require access to well-defined biological specimens from nonhuman disease. The above effort will likely require support from industry, private foundations and government agencies. Considering the burden of fibrosing lung disorders to both humans and domestic animals, such investment is considered worthy.

## MEETING PARTICIPANTS (SEE FIGURE 2)

Teresa Barnes Tosi, formerly of Coalition of Pulmonary Fibrosis, The Westie Foundation; Peter Bitterman, University of Minnesota; Kevin K. Brown, National Jewish Health; Tim Capps, University of Louisville; Stephan Carey, Michigan State; Mike Chaddock, Texas A&M University; Cecile Clercx, University of Liege; Alan Cohen, EddingPharm; Brendan Corcoran, University of Edinburgh; Joao deAndrade, University of Alabama-Birmingham; Jason DeVoss, Genentech; Dennis E. Doherty, University of Kentucky; Steven Dow, Colorado State University; Kari Ekenstedt, University of



**FIGURE 2.** Meeting participants.

Wisconsin; Valerie Fadok; Mostafa M. Fraig, University of Louisville; Marilyn Glassberg, University of Miami; Allyn Harris, University of Mississippi; Ann Marie Hollowathy, The Westie Foundation; Susan Johnson Rowland, Harvey Oaks Animal Hospital; Robert Kaner, Cornell University; Paula Katavolos, Genentech; Anne Keane, Genentech/Roche; Caroline Keane, Roche Welwyn, United Kingdom; Dolly Kervitsky, Pulmonary Fibrosis Foundation; Wayne Kompare, The Westie Foundation of America; Liisa Lilja-Maula, University of Helsinki; Andrew Limper, Mayo Clinic; Mahmoud Loghman-Adham, Baxter Healthcare; David Lynch, National Jewish Health; Clay Marsh, Ohio State University; Kay McGuire, The Westie Foundation; Ana Mora, University of Pittsburgh; Imre Noth, University of Chicago; Mitchell Olman, Cleveland Clinic; Amy Olson, National Jewish Health; Patricia Olson, Seattle, WA; Greg Cosgrove, National Jewish Health; Matt Huentelman, Tgen; David Schwartz, University of Colorado; Bebe Pinter, WFA; Andrew Tager, Massachusetts General Hospital; William Kurt, Michigan State; John Tosi, New York; Rick Vulliet, UC Davis; Mark Neff, Van Andel Institute; Carol Reiner, University of Missouri; Mauricio Rojas, University of Pittsburg; Chand Khanna, NIH; Elizabeth Rozanski, Tufts University; Elaine Ostrander, NIH; Rafael Perez, University of Louisville; Tamra Perez, University of Louisville, and Jesse Roman, University of Louisville.

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Huston). Allison Pratt assisted with artistic design of logo, Susie Stone created a website and Glenn Vicary helped with data collection. Symposium sponsors had no input in the development of the symposium content, selection of speakers, or in the development of this manuscript.

## CONFLICT OF INTEREST STATEMENT

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Pulmonary group of the American College of Chest Physicians. D.J.K reports personal fees from Boehringer-Ingelheim, outside the submitted work; and was formerly Vice President of Patient Relations and Medical Affairs at the Pulmonary Fibrosis Foundation. A.H.L. has served as site PI or collaborator on industry-sponsored clinical trials (Roche-Genentech, Boehringer Ingelheim) and has been funded by the National Institutes of Health and The Hurvis and Brewer Foundations. He has served on the Boards of the Pulmonary Fibrosis Foundation. K.W. has received research funding through the AKC Canine Health Foundation for a separate project. J.R. has served as site PI or collaborator in industry-sponsored clinical trials (Gilead, InterMune, ImmuneWorks, Boehringer Ingelheim, Bristol Myers Squibb) and is funded by the National Institutes of Health and the Department of Veterans Affairs. He served on the Boards of the Pulmonary Fibrosis Foundation and the American Lung Association-Midland States.

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