AMERICAN THORACIC SOCIETY DOCUMENTS

An American Thoracic Society Official Research Statement: Future Directions in Lung Fibrosis Research

Eric S. White, Zea Borok, Kevin K. Brown, Oliver Eickelberg, Andreas Guenther, R. Gisli Jenkins, Martin Kolb, Fernando J. Martinez, Jesse Roman, and Patricia Sime; on behalf of the American Thoracic Society Respiratory Cell and Molecular Biology Assembly Working Group on Pulmonary Fibrosis

This Official Research Statement of the American Thoracic Society (ATS) was Approved by the ATS Board of Directors, January 2016

ORCID ID: 0000-0003-4060-8443 (E.S.W.).

Background: Pulmonary fibrosis encompasses a group of lung-scarring disorders that occur owing to known or unknown insults and accounts for significant morbidity and mortality. Despite intense investigation spanning decades, much remains to be learned about the natural history, pathophysiology, and biologic mechanisms of disease.

Purpose: To identify the most pressing research needs in the lung fibrosis community and to provide a roadmap of priorities to investigators, funding agencies, patient advocacy groups, and other interested stakeholders.

Methods: An *ad hoc* international working group of the American Thoracic Society with experience in clinical, translational, and bench-based research in fibrotic lung diseases was convened. The group used an iterative consensus process to identify successes and challenges in pulmonary fibrosis research.

Measurements and Main Results: The group identified five main priority areas in which substantial resources should be invested to advance our understanding and to develop novel therapies for patients with pulmonary fibrosis. These priorities include develop newer models of human lung fibrosis, engage current and new stakeholders to provide sustained funding for the initiatives, create a global infrastructure for storing patient-derived materials, establish collaborative preclinical and clinical research networks in fibrotic lung disease, and create a global lung fibrosis initiative that unites these multifaceted efforts into a single virtual umbrella structure.

Conclusions: Despite recent advances in the treatment of some forms of lung fibrosis, many gaps in knowledge about natural history, pathophysiology, and treatment remain. Investment in the research priorities enumerated above will help address these shortcomings and enhance patient care worldwide.

Keywords: pulmonary fibrosis; patient advocacy; patient care; biomedical research; consensus

Contents

Overview

Research priorities are fluid, bowing to pressures such as prior scientific discoveries, funding availability, and technological advances, to name but a few. Over the past few years, the pulmonary fibrosis community has witnessed an expansion in

Supported by funding from the National Institutes of Health (E.S.W., Z.B., K.K.B., F.J.M., J.R., and P.S.); the U.S. Department of Veterans Affairs (J.R.); the Drews Family Sarcoidosis Research Fund (E.S.W.); the Will Rogers Institute and the Hastings Foundation (Z.B.); the Helmholtz Association and the German Center of Lung Research (O.E.); the German Research Council, Federal Ministry of Education and Research, State of Hesse (A.G.); the Wellcome Trust, the Medical Research Council, and the National Centre for Replacement, Reduction, and Refinement (R.G.J.); the Canadian Institute for Health Research, the Research Institute of St. Joe's Hamilton, and the Canadian Pulmonary Fibrosis Foundation (M.K.); and the Davis Endowment (P.S.).

Correspondence and requests for reprints should be addressed to Eric S. White, M.D., Division of Pulmonary and Critical Care Medicine, University of Michigan Medical School, Ann Arbor, MI. E-mail: docew@umich.edu

Am J Respir Crit Care Med Vol 193, Iss 7, pp 792–800, Apr 1, 2016

DOI: 10.1164/rccm.201602-0254ST
Internet address: www.atsjournals.org

its understanding of factors affecting the pathogenesis, development, and progression of fibrotic lung disease. We have also heralded the availability of two new medications for the treatment of idiopathic pulmonary fibrosis (IPF) (1, 2). However, more work is clearly needed to further our understanding of mechanisms of fibrogenesis and to enhance the translatability of scientific discoveries. Recently, the NHLBI convened a workshop to define priorities in specific areas of IPF research (3); similarly, a working group of the Respiratory Cell and Molecular Biology (RCMB) Assembly of the American Thoracic Society (ATS) convened a workshop to discuss comparative pathobiology of lung fibrosis between humans and domestic animals (4) as well as a conference to plan biorepository strategies among academic institutions, industry partners, patient advocacy groups, and government agencies (5). Complementary to these works, we convened an *ad hoc* subcommittee from the RCMB Working Group on Lung Fibrosis, composed of investigators with experience in bench-based, translational, and patient-based pulmonary fibrosis research, to enumerate and elaborate on conceptual priorities in pulmonary fibrosis research.

Our group initially met at the ATS International Conference in San Diego (May, 2014) to discuss prior research successes and current roadblocks to further progress. A second meeting was held at the International Colloquium on Lung and Airway Fibrosis in Mont Tremblant, Quebec, Canada (September, 2014), at which time subgroups were formed and tasked with researching and writing various sections of the document. The draft document was reviewed and edited by all members of the group. A third meeting at the ATS International Conference in Denver (May, 2015) was held to finalize the document. As a result of these meetings, the group identified the following major challenges:

- Current *in vivo*, *in vitro*, *ex vivo*, and *in silico* models of human lung fibrosis have been instrumental to our understanding of lung fibrogenesis but largely do not resemble human disease. This may be due to anatomic, age and/or functional differences among species and models, artificiality/duration of the initial fibrotic insult, nonphysiologic culture conditions, or lack of standardized endpoints, to name a few.
- Funding for pulmonary fibrosis research has been limited to traditional funding sources (e.g., government, advocacy groups, and industry support). Moving forward, these sources are likely to be insufficient to sustain the research endeavors necessary to drive the field forward.
- The infrastructure needed to conduct high-quality, patient-relevant research in fibrotic lung disease is suboptimal. Although individual researchers and centers may have access to patient-related materials and data, these samples are often unavailable to large portions of the scientific community, thereby hampering scientific progress. Additionally, quality of both data and matching samples may be limiting.
- Timely clinical study of potential therapeutics or diagnostics identified in preclinical research is hampered by difficulties faced by researchers in engaging centers with expertise in clinical study design and execution.
- Pulmonary fibrosis is rare and daunting to address for both patient and clinician. Despite the worldwide increasing incidence in lung fibrosis (and fibrosis of other organ systems) (6), a global approach to lung fibrosis research is lacking.

To confront these challenges, the group made the following recommendations:

- Define, create, and refine *in vivo*, *in vitro*, *ex vivo*, and *in silico* preclinical models that better recapitulate human lung fibrosis, as current models insufficiently resemble human disease. This includes detailed descriptive studies of normal and diseased human lungs using cutting-edge technologies not previously available.
- Engage traditional stakeholders (government, industry, foundations) and identify newer partners (e.g., Center for Medicare and Medicaid Services, private insurers, nongovernmental organizations, philanthropy) to provide sustained funding of lung fibrosis–based research (bench based, preventive, clinical, patient-reported outcomes, etc.).
- Create a multinational research platform capable of collecting (in a standardized fashion), storing, and distributing clinically annotated patient-derived samples in an open-access biorepository, including detailed exposure and clinical information.
- Establish a clinical research center network that can synergize efforts with preclinical investigators to enable rapid testing of the most promising compounds in a standardized and efficient fashion.
- Advocate nationally and internationally to develop a global lung fibrosis initiative to address the dilemma of lung fibrosis on a worldwide scale. This initiative could take advantage of current efforts to target fibrotic diseases in other organs by rapidly adopting them to lung fibrosis studies.

Introduction

Pulmonary fibrosis is defined as a chronic, frequently progressive, fibrosing interstitial lung disease (ILD) with few effective therapeutic options. Pulmonary fibrosis may occur as a result of occupational exposures (e.g., silica, beryllium), drug toxicity (e.g., methotrexate, amiodarone, nitrofurantoin), and connective tissue diseases (e.g., scleroderma), or it may be idiopathic in etiology (e.g., IPF). The incidence of IPF and other fibrotic disorders of lung is on the rise worldwide, likely affecting hundreds of thousands, or even millions, of patients globally (7). Although research efforts to date in the bench-based and clinic-based arenas have yielded much important information regarding potential etiologies, pathogenesis, natural history, and diagnostic approaches of various fibrotic lung diseases, there has not been a commensurate increase in therapeutic options or survival of these patients. Despite the approval by the U.S. Food and Drug Administration in October, 2014 of both pirfenidone and nintedanib for patients with IPF, no drug has conclusively been shown to improve survival or quality of life in patients with fibrotic lung disorders, despite a slowing of the rate of decline in FVC, leaving lung transplantation (which is limited to a minority of patients) as the only potentially life-prolonging treatment option (8).

Recently, the NHLBI convened a workshop to outline scientific topics that require further study in IPF, resulting in a workshop report enumerating specific scientific priorities (3). Related but separate reports focusing on fibrosis across various organ systems (G.P. Cosgrove and colleagues, unpublished material) and

pulmonary fibrosis across species (G. Vicary and colleagues, unpublished results) are currently being prepared. All reports define priority areas of scientific investigation in patients with IPF (although these priorities could be extended to all fibrotic lung diseases) but do not describe the means by which this research will proceed successfully. Thus, an *ad hoc* group of investigators with experience in bench-based, translational, and patient-based research was convened to identify strengths and challenges in performing pulmonary fibrosis research and to offer specific suggestions for enhancing future research endeavors in pulmonary fibrosis. This Research Statement will provide a forward-looking framework we believe to be critical to the advancement of lung fibrosis research, centered around five pillars: modeling lung fibrosis, engaging stakeholders, infrastructure development, establishing synergistic relationships between clinical and preclinical networks, and development of a global lung fibrosis initiative.

Methods

The project was initiated as an RCMB Assembly Project and approved by the ATS Project Review Subcommittee. Participants were each chosen by the Project Chair (E.S.W.) because of expertise in specific aspects of lung fibrosis research, program development, involvement with patient advocacy groups, and standing in the field. All participants were approved by the RCMB Planning Committee, the RCMB Executive Committee, and the ATS Project Review Subcommittee. International members were chosen to ensure a diverse representation.

The group initially met at the ATS International Conference in San Diego (May, 2014) to discuss prior research successes and current roadblocks to further progress. A second meeting was held at the International Colloquium on Lung and Airway Fibrosis in Mont Tremblant, Quebec (September, 2014), at which time subgroups were formed and tasked with researching and writing various sections of the document. The draft document was reviewed and edited by all members of the group. A final meeting at the ATS International Conference in Denver (May, 2015) was held to finalize the document.

Literature searches were conducted by several group members using traditional biomedical search engines and formal and informal discussions among thought leaders in pulmonary fibrosis research, including bench and clinical investigative academicians in the United States and abroad, patient advocacy representatives, representatives from funding agencies, and pharmaceutical representatives, were undertaken. Recommendations were formulated, and differences were resolved by discussion and iterative consensus (Table 1).

Potential conflicts of interest were disclosed and vetted in accordance with the policies and procedures of the ATS. The ATS has analyzed this document and its authors' financial disclosures for commercial bias. Several authors have research support or other involvement with industry relevant to lung fibrosis research. The authors have recommended increased industry support of academic lung fibrosis research in general. The ATS views this recommendation and all other recommendations within as appropriate and necessary.

Modeling Lung Fibrosis

Models of lung fibrosis use *in vitro*, *ex vivo*, *in silico*, and *in vivo* approaches. The group recognizes that although all fibrosis models have scientific value, no single model currently recapitulates all salient features of human disease. Multiple models should be used routinely when testing hypotheses regarding disease pathogenesis or treatment approaches, with the choice of model dependent on the scientific question being posed. This should be accomplished within a "preclinical research network" of centers that rapidly and reliably test putative interventions in a wide variety of complementary models simultaneously (e.g., *in vivo* animal model, *ex vivo* lung slice, *in vitro* cell assays) challenged with various insults appropriate to the scientific question being asked (e.g., bleomycin, silica, radiation, or virus-induced fibrosis). Features of rodent and other animal models of lung fibrosis vary depending on the insult, timing, and strain of animal (reviewed in References 4, 9–11). In this fashion, drugs or other interventions shown to be efficacious in multiple models could be candidates to be tested in a "clinical research network" (CRN) (*see* Establishing Synergistic Relationships between Clinical and Preclinical Networks). Moving forward, however, emphasis should also be placed on creating more biologically relevant models of human lung fibrosis.

The ideal model of human lung fibrosis will be characterized by multiple features: it will be clinically relevant to human anatomy and physiology; it will replicate salient aspects of human disease with regard to initiation, pathology (e.g., fibroblastic foci and microscopic honeycombing in the case of usual interstitial pneumonia), disease

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
Searched multiple electronic databases	x	
Reviewed reference list of retrieved articles	x	
Evidence synthesis		
Applied preselected inclusion and exclusion criteria		x
Evaluation included articles for sources 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; NA = not applicable; PRISMA1 = Preferred Reporting Items for Systematic Reviews and Meta-Analyses 1.
*Not required for research statements.

progression, and age of onset and sex preference; it will allow assessment of contributions from and interactions among various different cell types (including epithelium, fibroblasts, inflammatory cells and endothelial cells) and via various molecular pathways; it will allow testing of reversibility of fibrosis, preferably in the form of a high-throughput screen; it will incorporate cofactors such as environmentally relevant exposures, work-related factors, and the microbiome, which are not considered with current specific pathogen-free models; it should be widely accessible to researchers worldwide; it should be relatively simple to incorporate into current research endeavors; and it should be relatively inexpensive.

Experimental evidence suggests that multiple molecular pathways can lead to the development of lung fibrosis; thus, modeling should also seek to explore the pleiotropic nature of fibrogenesis. To that end, models that are capable of investigating multiple biologic processes simultaneously are more likely to provide insights into human disease pathogenesis. Such a "multiple hit" hypothesis has been forwarded for many ILDs, such as hypersensitivity pneumonitis (12), sarcoidosis (13), and IPF (14). Determining whether this hypothesis is true will require models that take multiple genetic, environmental, and host immunological aberrations into account.

We acknowledge that these are lofty goals that will require significant resources to develop, and we agree that initial iterations of the models will possess only a subset of these qualities. However, the group also feels strongly that the overall cost of developing such models will be recouped many times over by avoiding the expense associated with performing large clinical trials based on current modeling strategies. If the models provide valid, reproducible, and clinically relevant insights into human lung fibrosis, one can envision answering important ongoing questions in human lung fibrosis, such as identifying triggers that initiate fibrosis versus those that exacerbate fibrosis, understanding how normal resolution of lung injury differs from fibrotic resolution, and testing new therapeutic options. We, therefore, recommend:

- Assemble a preclinical research network of centers with proven expertise in fibrosis research that are willing and capable of performing intervention studies in an efficient and timely manner. Such a network could be assembled as a consortium, in which potential network center applications are reviewed by a study section, with a renewal process every 5 years.
- Conduct detailed, descriptive studies, leveraging cutting-edge technologies (e.g., microbiome analyses, quantitative proteomics, single-cell RNA-Seq) with the purpose of cataloging cells, extracellular matrix, biomechanical properties, and regional differences (e.g., upper versus lower lobe, distal versus proximal segments) to better understand the normal and diseased human lung.
- Develop newer models that better resemble human lung fibrosis, such as larger animal systems with lungs more similar to human lungs (e.g., ferret, pig, sheep), spontaneously occurring models of lung fibrosis (e.g., West Highland White Terriers), *ex vivo* perfusion of human and animal lungs, newer genetic models, and nanofabrication of biomimetic materials.
- Define appropriate endpoints (i.e., biochemical, imaging, functional) in various models that more accurately reflect degree of fibrogenesis, matrix turnover, and functional consequences of fibrosis.

Engaging Stakeholders to Identify Novel Sources of Research Funding

Large investments have been made directed at improving understanding of lung fibrogenesis through exploration of cellular pathways of inflammation, fibroproliferation, and tissue remodeling; characterization and study of animal models of lung fibrosis; and investigation of treatments in clinical trials. Despite this investment, the incidence of fibrotic lung diseases continues to increase (15–17), total healthcare expenditures for patients with pulmonary fibrosis are high (18, 19), hospitalization rates appear to be increasing (20, 21), and mortality rates remain elevated in both sexes (8). Lung transplantation, considered the most effective treatment for end-stage fibrotic lung disease, is not without complications and is only available to a minority of patients. Recently approved drugs are suboptimal (1, 2), necessitating further research aimed at not only halting progression or reversing fibrosis but also primary prevention. Indeed, the NHLBI has recently launched an initiative addressing this very issue (22), and for the vast majority of occupational ILDs, primary prevention may ultimately be the most effective intervention. Regardless of the approaches taken, it is safe to conclude that the human and economic burden of fibrotic lung disease will continue to rise worldwide for decades to come unless we redouble our efforts directed at defining its etiology, elucidating mechanisms involved in its development and progression, and unveiling safe and effective treatments capable of improving quality of life and survival. Any advancement in this area is likely to be applicable to fibrosing conditions of other organs.

Over the past 3 decades, the cost of pulmonary fibrosis research has likely reached billions of dollars; some estimates place National Institutes of Health (NIH) expenditures in this area at tens of millions of dollars annually. Yet considering the gaps in knowledge that remain and the continuing burden of pulmonary fibrosis worldwide, we must sustain (if not increase) this effort. Competing (and worthy) research related to other more prevalent lung disorders and other diseases further dilute current resources for research funding. Nevertheless, it is imperative that we continue to work toward raising awareness about pulmonary fibrosis, identifying alternative sources for research funding, and, ultimately, developing a united front to provide "a face" to this condition for potential stakeholders. The following recommendations address these areas:

- Carefully design studies to determine the true burden of fibrotic lung disease regarding quality of life (through creation of robust and valid instruments specific for ILD), healthcare resource use (surveying practice patterns for longitudinal physiologic and radiologic testing), and overall impact to the economy. Studies are needed to convince funding agencies to align resource allocation with disease burden. With healthcare reform initiatives in the United States and other countries, and the importance of value and quality care, understanding these issues will require new efforts and additional funding.
- Revamp lobbying efforts targeting traditional funding agencies in the United

States and abroad (e.g., NIH, Medical Research Council, INSERM, Canadian Institute of Health Research, German Center for Lung Research, Science Foundation Ireland) to raise awareness about pulmonary fibrosis. Coordinated education of the public, healthcare workers, and funding agencies about pulmonary fibrosis will be instrumental. It is critical that the pulmonary fibrosis community learns to lobby more persistently and effectively to key stakeholders, including congressional officials with the assistance of partner organizations, and media outlets to help promote awareness.

- Identify alternative sources of funding to sustain high-impact efforts in pulmonary fibrosis research, which is often quite costly. In addition to the U.S. NIH, other government agencies should be considered, including the Food and Drug Administration and the Department of Defense. Similar agencies in other countries should also be considered. With its large numbers of aging veterans, the Department of Veterans Affairs represents yet another source of possible investment. Other potential sources include investment by insurers (both private and public) interested in improving the care of patients they serve or by industry groups with whom lung fibrosis is associated (e.g., coal, tobacco, foundry, etc.), funding research designed to identify best practices that improve quality of life and provide value care. Finally, partnerships among academia, foundations, and the pharmaceutical industry remain important and should be strengthened.

Infrastructure

The field of pulmonary fibrosis research has benefited from a tremendous increase in the number of treatment trials, cohort studies, and available datasets over the last decade; however, many questions remain unanswered. The best quality datasets usually arise from multicenter, prospective, randomized clinical trials. Truly enhancing clinical research in pulmonary fibrosis will require a substantial infrastructure that identifies patients, organizes research protocols, and collects data and biomaterials in a standardized, protocol-driven way. Ultimately, this approach will allow the application of precision medicine approaches to treat patients with lung fibrosis. However, the infrastructure necessary to accomplish this in a coordinated fashion—the institutions that will register patients into databases/registries, development of standardized protocols for acquisition of samples and clinical data, the physical space to collect and store biological samples, the personnel needed to collect and input longitudinal clinical data—is nonexistent (5). Although certain individual centers may have expertise in this arena, impactful advances are more likely to occur when a robust clinical database coupled with biologic samples across centers can be directly queried, thereby enriching the accessible data to investigators the world over. The European IPF Registry and Biobank (www.pulmonary-fibrosis.net; currently comprising 1,800 patients) is probably the only truly international registry that also samples biomaterials in subjects with idiopathic interstitial pneumonia. Although implemented within the seventh Framework Program for Research and Technological Development through the European Commission and now superseded by Horizon 2020, the biobank will prove difficult to expand to translational research activities and to maintain high-level phenotyping in the absence of sustained funding.

We therefore strongly endorse the concept of a multistakeholder clinical research center network and believe that investment in this infrastructural component of a pulmonary fibrosis open-source human research library is critical to expand access to tissues and generated data for understanding pathogenesis, identifying new pathways instrumental in disease progression and drug development in adequately powered experiments. Without an organized and efficient clinical research infrastructure, longitudinal cohorts (from whom natural, work and environmental exposure information, and prognostic biomarker studies can be obtained) will continue to suffer from limited size, power, and heterogeneous characterization, and potential sponsors of clinical trials may decide to look to other diseases where the feasibility of successful trial conduct seems greater.

The group made the following recommendations:

- Establish an open-access, national (and ultimately global) biorepository of biologic samples (primary cells, tissue blocks, genetic material, bronchoalveolar lavage fluid, whole blood, plasma, serum, peripheral blood mononuclear cells) from patients with pulmonary fibrosis, coupled with longitudinal clinical and job exposure data (5). Samples and clinical data must be freely available but also must be scientifically justified.
- Participating donors to this resource will need to agree *a priori* on protections of intellectual property rights and licensing rights of any discoveries made using samples provided by such a biorepository.
- Widespread agreement on types of clinical and exposure data, frequency with which it is collected, and protocols for obtaining such data will need to be achieved. Informed consent documents for clinical trials moving forward must be aligned with both the purpose of the clinical study and the biorepository, including specific consent for genetic studies. Careful attention to protection of patient confidentiality will be of the utmost importance.

Establishing Synergistic Relationships between Clinical and Preclinical Networks

The research infrastructure described earlier, although central to future studies in pulmonary fibrosis, would be incomplete without a link to a robust CRN, a consortium of clinical centers and other stakeholders dedicated to the design and conduct of patient-centered research. As first demonstrated by the NHLBI-sponsored IPFnet (Idiopathic Pulmonary Fibrosis Network) (23, 24), a precursor network that focused primarily on the design and conduct of late-phase clinical trials, collaborative research efforts in fibrotic lung diseases can be highly effective in bringing investigators together and fostering scientific discovery. Such an approach would allow the development of standardized methodological collection of longitudinal clinical and biological data collection, centralized data management across multiple centers, provision of a collaborative clinical center network for efficient implementation of early- and late-phase clinical trials, creation of a governance structure that promotes

merit-based prioritization of resources and protocols, and promotion of standard of care practices to clinicians on the basis of evidence generated from comparative effectiveness and other outcomes research as alluded to in the prior section.

A centralized approach to clinical research would allow for standardization and prioritization of patient-based research activities leading to increased efficiency and economy of effort (including identifying optimal trial endpoints, markers of disease progression, and patient-reported outcome instruments). A centralized registry and biorepository would provide a global resource for scientists and allow comparisons across studies that are currently impossible. As more sponsors develop protocols to test novel compounds, and as trials move from placebo controlled to those including approved therapies with larger sample sizes, it will be essential to organize the clinical trial activities of the lung fibrosis community to efficiently identify and enroll patients in the most promising studies. Moreover, this entity would be tasked with identifying optimal design strategies and endpoints in clinical trials to improve efficiency. Although the cost is significant, the need for a large, multicenter CRN may be greater now than it was before the availability of approved therapies. A network of centers with a common interest and experience in clinical research could bring together in partnership patients, clinicians, researchers, advocacy organizations, governmental agencies, and the pharmaceutical industry to provide a stable and strong foundation for future advances. We therefore recommend:

- Assembling a true ILD CRN that will link invested centers together for purposes of clinical research and synergize with preclinical investigators for participation in both bench-to-bedside and bedside-to-bench research. Assembly of such a network will be complex; prospectively defined entry criteria, conflict-resolution strategies, and information dissemination practices will need careful consideration.
- Creating standardized practices for clinical research trials in ILD, including appropriate trial design, comparators, and endpoints (e.g., physiologic, radiologic, survival). This should also include an appropriate emphasis on identifying and validating quality-of-life measures for patients.
- Archiving clinically obtained data to support research in: improving quality of life and outcomes (clinical and patient-reported) of patients with ILD; identifying differing practice patterns for patients with ILD; enhancing diagnostic modalities; understanding natural history of different ILDs at various stages of disease; enhancing understanding of the epidemiology of environmental causes of ILDs; and improving awareness of, and enrollment in, clinical trials in ILD.

Development of a Global Lung Fibrosis Initiative

Reports summarizing the incidence and prevalence of pulmonary fibrosis have surfaced from the United States, United Kingdom, Czech Republic, Norway, Finland, Greece, Turkey, Japan, and Taiwan, among other countries (reviewed in Reference 25). Together, these and other studies emphasize the fact that lung fibrosis is a global healthcare problem affecting hundreds of thousands (if not millions) throughout the world. Because of its global impact, research directed at improving understanding about lung fibrogenesis is being conducted by investigative teams in many countries, and multicenter/multinational clinical trials in pulmonary fibrosis have become the standard when studying new treatments. Fibrosis research has unveiled promising targets for intervention, and many treatment strategies are currently undergoing early clinical testing or are waiting in the pipeline. These events, together with the hard work of lung fibrosis advocacy organizations and the recent approval of two new drugs for the treatment of IPF, have raised awareness about fibrotic lung diseases and their health burden worldwide. National funding agencies have increased their allocation of resources to pulmonary fibrosis research and private foundations focused on lung fibrosis have sprouted in many countries.

The above observations emphasize the need to coordinate patients with lung fibrosis and research on a multinational scale. Considering the global impact of this condition, the recognition that multinational clinical trials are needed to test new treatment strategies effectively, and the understanding that "big science" and "big data analysis" are more optimally conducted through large cooperative investigative (preferably international) networks, the need to develop a more organized, concerted global effort targeting pulmonary fibrosis now seems imperative. We recognize that differences in legislation across countries with respect to personal data management are major obstacles to moving this forward; politicians and other lawmakers around the world should be made aware of the need for less restrictive sharing of data while simultaneously strengthening patient protections for personal health information.

A global lung fibrosis initiative should follow the lead of more prevalent pulmonary conditions, such as the GOLD (Global Initiative for Chronic Obstructive Lung Disease) in chronic obstructive pulmonary disease (26) and the GINA (Global Initiative on Asthma) (27), although we recognize that the initial focus may be slightly different given the relative paucity of treatment options in fibrotic lung disease and the lack of standardized treatment approaches. The group recommends:

- A worldwide effort focusing on defining the true incidence and prevalence of all forms of fibrotic lung disease (not just IPF) as well as the natural history of these diseases. Such efforts should emphasize (*1*) understanding the burden of disease among underserved populations in the United States and abroad; (*2*) environmental and occupational exposures, socioeconomic and other risk factors that predispose to development of fibrotic lung diseases; and (*3*) predilection of diseases between sexes and among races and ethnicities.
- Promoting further etiologic and epidemiologic research to identify modifiable risk factors. With the recognition that environmental exposures to toxic chemicals, inorganic and organic dusts, and biomass smoke (among others) may lead to pulmonary fibrosis, a global lung fibrosis initiative should also serve to address the primary prevention of fibrotic lung disease, similar to global efforts to better understand and prevent chronic obstructive pulmonary disease.
- Formation of a global initiative to collect, properly and carefully annotate, and share patient-derived samples for investigative research. One such example is a

worldwide effort (including sites from North America, Europe, Asia, and South/Central America) designed to collect DNA and clinical data from 10,000 individuals with IPF for studies regarding genetic predispositions to IPF (David A. Schwartz, M.D., personal communication). These efforts should also be expanded to other fibrotic diseases and other patient-derived samples.

Rare disease communities, such as pulmonary arterial hypertension, have benefited greatly from global efforts (e.g., the World Health Organization World Symposium on Pulmonary Hypertension [28]); it is a reasonable expectation that the lung fibrosis community will see similar benefits. Additional benefit will come from the coordinated effort of patient advocacy groups and healthcare professionals to educate the public about the dangers of lung fibrosis, its impact on overall health, and the need for further research in this arena.

We envision a global lung fibrosis initiative that will serve as the umbrella entity for worldwide efforts in: (*1*) developing a pulmonary fibrosis patient registry and identifying at risk cohorts, (*2*) creating a data and tissue biorepository, (*3*) fostering a disease modeling and stratification network, (*4*) building a clinical trials network, (*5*) enhancing patient care and research advocacy efforts, and (*6*) cultivating a global education/outreach program (endorsed by the World Health Organization and international advocacy groups) to educate patients, families, and clinicians about the need for further lung fibrosis research. The message needs to emphasize the purpose of our mission of eradicating fibrotic lung disease: one world, one goal.

The governing structure of a global lung fibrosis initiative may take many forms (one example is seen in Figure 1) and would be composed of representatives from each of the major stakeholders in pulmonary fibrosis research and clinical care as described within this document. This structure will be necessary for facilitating decision making, prioritizing the agenda, determining allocation of resources, and coordinating interactions with partners.

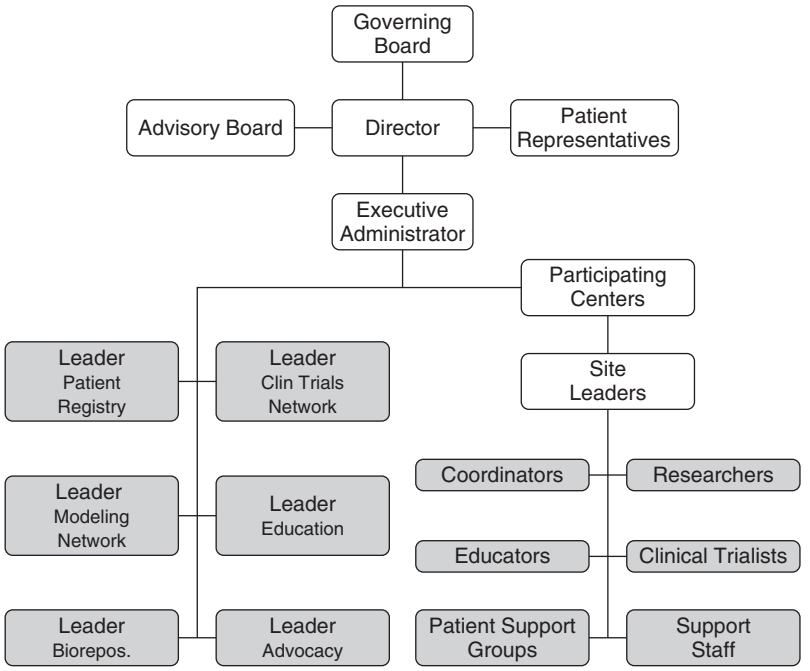

Figure 1. Example of a governing schematic for a global lung fibrosis initiative. Input from patient representatives, an advisory board, and a governing board would provide overall direction and administration of the initiative to harmonize the goals of addressing the various aspects of lung fibrosis research. Other governance structures may be suitable to achieve the same goal.

Summary

Much progress has been made in the field of pulmonary fibrosis research and clinical care. But like all good research, this progress has raised more questions; prior efforts have been undertaken to identify gaps in our knowledge about lung fibrosis both clinically and scientifically (3). Logistically, succeeding in moving forward will require securing adequate funding from multiple traditional and newer sources to support the development of newer models of human lung fibrosis, the clinical and preclinical infrastructure to support efficient translation of promising molecules from the bench to the clinic, further epidemiologic studies to define modifiable risk factors, and the education and outreach efforts needed to enhance global awareness of pulmonary fibrosis. This is an ambitious agenda, but we believe it is vital to make the necessary steps forward for patients and their families. ■

This research statement was prepared by the American Thoracic Society Respiratory Cell and Molecular Biology Assembly Working Group on Pulmonary Fibrosis.

Members of the working group are as follows:

Eric S. White, M.D. (*Chair*)
Zea Borok, M.B., Ch.B.
Kevin K. Brown, M.D.
Oliver Eickelberg, M.D.
Andreas Guenther, M.D.
R. Gisli Jenkins, Ph.D.
Martin Kolb, M.D., Ph.D.
Fernando J. Martinez, M.D., M.S.
Jesse Roman, M.D.
Patricia Sime, M.D.

Author Disclosures: K.K.B. served on advisory committees for Aeolus, AstraZeneca, Centocor, Fibrogen, Galecto, GeNO, Genoa, Gilead, MedImmune, Prometic Life Sciences, Promedior, and Veracyte; on an advisory committee and data and safety monitoring board for Biogen Idec; on an advisory committee and as a consultant for Boehringer Ingelheim; and as a consultant for Altitude, Bayer HealthCare, Celgene, Genentech USA, Genzyme, GlaxoSmithKline,

ImmuneWorks, Mesoblast, Moerae, Novartis, PharmAkea, and Pfizer. A.G. served on advisory committees for Actelion, Boehringer Ingelheim, InterMune, Novartis, and Pfizer; and as a consultant for Activaero and Nycomed. R.G.J. served on advisory committees for Boehringer Ingelheim, InterMune, PharmAkea, Pulmatrix, and Roche; served on an advisory committee for and received research support from Biogen Idec, GlaxoSmithKline, and MedImmune; and received research support from Galecto, Novartis, and Nuformix. M.K. served on an advisory committee for AstraZeneca; received research support from Actelion, Boehringer Ingelheim, Gilead, Janssen, and Prometic Life Sciences; served as a consultant for Boehringer Ingelheim International, F. Hoffmann-La Roche, Gilead, GlaxoSmithKline, Janssen, and Prometic Life Sciences; and served as a speaker for Boehringer Ingelheim International and F. Hoffmann-La Roche. F.J.M. served on advisory committees for AstraZeneca, Boehringer Ingelheim, Genentech, GlaxoSmithKline, Novartis, Pearl, Pfizer, Sunovion, and Veracyte; as a consultant for Able, American Institute of Research, Amgen, Axon, Bayer HealthCare, Bellerophon, Carden Jennings, CSA Medical, Forest, Hoffmann-La Roche, inThought, Janssen, Johnson and Johnson International, Kadman, Medical Leverage (Unity), Merck Sharp & Dohme, Skyepharma, Takeda, and Theravance Biopharma; received research support from Centocor, Gilead, and Takeda; served as a speaker for AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, and Takeda; served on a data and safety monitoring board for Biogen Idec; and consulted on "FDA Mock boards" for Boehringer Ingelheim and GlaxoSmithKline. J.R. served on a data and safety monitoring board for Boehringer Ingelheim, Fibrogen, Gilead, and InterMune. P.S. served as a consultant for Boehringer Ingelheim, Galecto, InterMune, and Prometic Life Sciences; on advisory committees for Galecto and Maresins; and on a data and safety monitoring board for InterMune. E.S.W., Z.B., and O.E. have no relevant commercial interests.

Acknowledgment: The authors thank the members of the American Thoracic Society Environmental, Occupational, and Population Health Assembly (Dr. Robert Tighe [Duke University, Durham, NC], Dr. Carrie Redlich [Yale University, New Haven, CT], and Dr. Jack Harkema [Assembly Chair; Michigan State University, East Lansing, MI]) for their critical input and Dr. Bruno Crestani (Hôpital Bichat Paris, Paris, France), Dr. Andrew Tager (Massachusetts General Hospital, Boston, MA), Dr. Hal Collard (University of California, San Francisco, CA), Dr. Philippe Bonniaud (Centre Hospitalier Universitaire, Dijon Bourgogne, France), Dr. Michael Keane (University College Dublin, Ireland), Dr. Toby Maher (The Royal Brompton Hospital, London, UK), and Dr. Gregory Cosgrove (National Jewish Health, Denver, CO and Chief Medical Officer, Pulmonary Fibrosis Foundation) for their analytical review of the manuscript and constructive suggestions.

References

1. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, Cottin V, Flaherty KR, Hansell DM, Inoue Y, *et al*.; INPULSIS Trial Investigators. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med* 2014;370:2071–2082.
2. King TE Jr, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, Gorina E, Hopkins PM, Kardatzke D, Lancaster L, *et al*.; ASCEND Study Group. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 2014;370: 2083–2092.
3. Blackwell TS, Tager AM, Borok Z, Moore BB, Schwartz DA, Anstrom KJ, Bar-Joseph Z, Bitterman P, Blackburn MR, Bradford W, *et al*. Future directions in idiopathic pulmonary fibrosis research: an NHLBI workshop report. *Am J Respir Crit Care Med* 2014;189:214–222.
4. Roman J, Brown KK, Olson A, Corcoran BM, Williams KJ; ATS Comparative Biology of Lung Fibrosis Working Group. An official American thoracic society workshop report: comparative pathobiology of fibrosing lung disorders in humans and domestic animals. *Ann Am Thorac Soc* 2013;10:S224–S229.
5. White ES, Brown KK, Collard HR, Conoscenti CS, Cosgrove GP, Flaherty KR, Leff JA, Martinez FJ, Roman J, Rose D, *et al*. Open-access biorepository for idiopathic pulmonary fibrosis: the way forward. *Ann Am Thorac Soc* 2014;11:1171–1175.
6. Cox TR, Erler JT. Remodeling and homeostasis of the extracellular matrix: implications for fibrotic diseases and cancer. *Dis Model Mech* 2011;4:165–178.
7. Hubbard R, Johnston I, Coultas DB, Britton J. Mortality rates from cryptogenic fibrosing alveolitis in seven countries. *Thorax* 1996; 51:711–716.
8. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, Colby TV, Cordier JF, Flaherty KR, Lasky JA, *et al*.; ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/ JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011;183:788–824.
9. Moore BB, Hogaboam CM. Murine models of pulmonary fibrosis. *Am J Physiol Lung Cell Mol Physiol* 2008;294:L152–L160.
10. Pauluhn J, Baumann M, Hirth-Dietrich C, Rosenbruch M. Rat model of lung fibrosis: comparison of functional, biochemical, and histopathological changes 4 months after single irradiation of the right hemithorax. *Toxicology* 2001;161:153–163.
11. Verkman AS. From the farm to the lab: the pig as a new model of cystic fibrosis lung disease. *Am J Physiol Lung Cell Mol Physiol* 2008; 295:L238–L239.
12. Selman M, Pardo A, King TE Jr. Hypersensitivity pneumonitis: insights in diagnosis and pathobiology. *Am J Respir Crit Care Med* 2012; 186:314–324.
13. Culver DA, Newman LS, Kavuru MS. Gene-environment interactions in sarcoidosis: challenge and opportunity. *Clin Dermatol* 2007;25: 267–275.
14. Thannickal VJ, Zhou Y, Gaggar A, Duncan SR. Fibrosis: ultimate and proximate causes. *J Clin Invest* 2014;124:4673–4677.
15. Raghu G, Weycker D, Edelsberg J, Bradford WZ, Oster G. Incidence and prevalence of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2006;174:810–816.
16. Olson AL, Swigris JJ. Idiopathic pulmonary fibrosis: diagnosis and epidemiology. *Clin Chest Med* 2012;33:41–50.
17. Navaratnam V, Fleming KM, West J, Smith CJ, Jenkins RG, Fogarty A, Hubbard RB. The rising incidence of idiopathic pulmonary fibrosis in the U.K. *Thorax* 2011;66:462–467.
18. Collard HR, Ward AJ, Lanes S, Cortney Hayflinger D, Rosenberg DM, Hunsche E. Burden of illness in idiopathic pulmonary fibrosis. *J Med Econ* 2012;15:829–835.
19. Collard HR, Chen SY, Yeh WS, Li Q, Lee YC, Wang A, Raghu G. Health care utilization and costs of idiopathic pulmonary fibrosis in U.S. Medicare beneficiaries aged 65 years and older. *Ann Am Thorac Soc* 2015;12:981–987.
20. Navaratnam V, Fogarty AW, Glendening R, McKeever T, Hubbard RB. The increasing secondary care burden of idiopathic pulmonary fibrosis: hospital admission trends in England from 1998 to 2010. *Chest* 2013;143:1078–1084.
21. Durheim MT, Collard HR, Roberts RS, Brown KK, Flaherty KR, King TE Jr, Palmer SM, Raghu G, Snyder LD, Anstrom KJ, *et al*.; IPFnet investigators. Association of hospital admission and forced vital capacity endpoints with survival in patients with idiopathic pulmonary fibrosis: analysis of a pooled cohort from three clinical trials. *Lancet Respir Med* 2015;3: 388–396.
22. Pittman JE, Cutting G, Davis SD, Ferkol T, Boucher R. Cystic fibrosis: NHLBI Workshop on the Primary Prevention of Chronic Lung Diseases. *Ann Am Thorac Soc* 2014;11:S161–S168.
23. The IPFnet strategy: creating a comprehensive approach in the treatment of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2010;181:527–528.

24. Raghu G; IPFnet. Improving the standard of care for patients with idiopathic pulmonary fibrosis requires participation in clinical trials. *Chest* 2009;136:330–333.
25. Nalysnyk L, Cid-Ruzafa J, Rotella P, Esser D. Incidence and prevalence of idiopathic pulmonary fibrosis: review of the literature. *Eur Respir Rev* 2012;21:355–361.
26. Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS; GOLD Scientific Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. *Am J Respir Crit Care Med* 2001;163: 1256–1276.
27. Bousquet J. Global initiative for asthma (GINA) and its objectives. *Clin Exp Allergy* 2000;30:2–5.
28. Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, Gomez Sanchez MA, Krishna Kumar R, Landzberg M, Machado RF, *et al*. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2013 62: D34–D41.