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WORKSHOP REPORT

Pulmonary Fibrosis Stakeholder Summit

A Joint NHLBI, Three Lakes Foundation, and Pulmonary Fibrosis Foundation Workshop Report

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Abstract

Despite progress in elucidation of disease mechanisms, identification of risk factors, biomarker discovery, and the approval of two medications to slow lung function decline in idiopathic pulmonary fibrosis and one medication to slow lung function decline in progressive pulmonary fibrosis, pulmonary fibrosis remains a disease with a high morbidity and mortality. In recognition of the need to catalyze ongoing advances and collaboration in the field of pulmonary fibrosis, the NHLBI, the Three Lakes Foundation, and the Pulmonary Fibrosis Foundation hosted the Pulmonary Fibrosis Stakeholder Summit on November 8–9, 2022. This workshop was held virtually and was organized into three topic areas: *1*) novel models and research tools to better study pulmonary fibrosis and uncover new therapies, *2*) early disease risk factors and methods to improve diagnosis, and *3*) innovative approaches toward clinical trial design for pulmonary fibrosis. In this workshop report, we summarize the content of the presentations and discussions, enumerating research opportunities for advancing our understanding of the pathogenesis, treatment, and outcomes of pulmonary fibrosis.

Keywords: interstitial lung disease, pulmonary fibrosis

In 2012, the NHLBI conducted a workshop to define areas of future research direction in idiopathic pulmonary fibrosis (IPF) (1). The subsequent decade saw major advances in the understanding of disease pathogenesis, identification of molecular mediators promoting fibrosis, elucidation of genetic risk factors, development of imaging-based biomarkers, defining the risk of combined immunosuppression in patients with IPF, and demonstration of the efficacy of nintedanib and pirfenidone for slowing lung function decline in patients with IPF and those with other forms of progressive interstitial lung disease (ILD). Despite this, pulmonary fibrosis remains a disease with a high morbidity and mortality; currently approved therapies only slow the rate of disease progression (2–4). Significant work is required to ensure timely diagnosis of individuals with pulmonary fibrosis, identify treatments that will halt or reverse fibrosis, and improve the lives of individuals living with this disease.

On November 8–9, 2022, the NHLBI, the Three Lakes Foundation, and the Pulmonary Fibrosis Foundation convened the Pulmonary Fibrosis Stakeholder Summit. The goal of this summit was to identify scientific gaps and future basic and clinical research directions related to pulmonary fibrosis. This virtual summit was divided into three sessions addressing topics related to *1*) novel models and research tools to better study pulmonary fibrosis and uncover new therapeutic targets, *2*) early disease risk factors and methods to improve diagnosis, and *3*) innovative approaches to clinical trial design for pulmonary fibrosis. The topics for presentation were selected by the summit organizers, and efforts were made to have a broad representation of content and speakers. Here we summarize the content of the summit and present future research opportunities identified by collective discussion.

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Novel Models and Research Tools to Better Study Pulmonary Fibrosis and Uncover New Therapies

Despite numerous experimental studies describing the efficacy of novel compounds for reducing fibrosis, therapies that halt or reverse pulmonary fibrosis in patients remain elusive. The limitations of traditional models of pulmonary fibrosis to recapitulate human lung architecture and cellular composition and reflect the phenotypic and mechanistic features of human disease have been a major hurdle hampering drug development. The ability to model the highly complex biological phenomena of pulmonary fibrosis is crucial to better understand the biology of the disease, identify new drug targets, and test the efficacy of novel or repurposed compounds (5, 6).

Novel Animal Models

There is ongoing work to develop models that more accurately mirror the evolution from early injury through fibrogenesis to resolution. Moreover, animal models to study nonresolving, progressive fibrosis and early disease time points are also needed. Ferrets may serve as a model for studying a persistent fibrotic phenotype and elucidating the connection between MUC5B expression and abnormal lung remodeling. A gain-of-function *MUC5B* promoter variant is recognized as the dominant genetic risk factor in IPF, and ferrets have a distribution of MUC5B-producing submucosal glands similar to humans and express high amounts of *MUC5B* with native presence of the risk-conferring rs35705950 TT promoter variant (7). Human cell types, absent in mice, that participate in aberrant repair have also been identified in ferrets (8). Ferrets exposed to bleomycin exhibit persistent fibrosis with histopathology like human IPF with prominent airway remodeling, proximalization of the distal airway spaces, and MUC5B-rich honeycomb cystic structures that resemble honeycomb cysts in humans (7, 9). Limitations to the ferret model include increased cost and model complexity because of longer ferret lifespan, fewer ferret-specific reagents, and need for more drug compound in therapeutic experiments than in murine models.

Genetic models with intrinsic defects may enable early events in the fibrosis cascade culminating from epithelial cell dysfunction to be studied; these may better mimic pulmonary fibrosis initiation in humans. Mutations in the alveolar epithelial type 2 (AT2) cell restricted surfactant protein C (SP-C) gene (*SFTPC*) have been identified in a subset of patients with IPF (10). *Sftpc* mouse models, such as knock-in murine models expressing either a trafficking ($SP\text{-}C^{I73T}$) or a BRICHOS misfolding ($SP\text{-}C^{C121G}$) mutation, offer an additional and disease-relevant preclinical platform to explore IPF pathogenesis and therapeutic discovery (11, 12). Expression of either mutation in adult mice results in spontaneous fibrosis and recapitulates many disease-defining elements, including activation of lung tissue repair-associated pathways, heterogeneous fibrotic histology with features of usual interstitial pneumonia, restrictive lung physiology, and elevation of relevant IPF biomarkers (i.e., MMP7) (11, 12).

Despite the recognition of the need for novel models, traditional murine models continue to offer vast opportunities to study mechanisms driving pulmonary fibrosis and could importantly assist in the interrogation of the findings elucidated by single-cell profiling (13). Murine models enable genetic manipulation or deletion of cell lines and can be used to delineate the roles of specific fibroblast states, macrophage subtypes, and endothelial or epithelial cells within tissue injury and repair. These genetic models could then be shared with the research community more easily and at a lower cost than many other novel models to catalyze discovery.

Three-Dimensional Models of Pulmonary Fibrosis

Lung tissue–based precision-cut lung slices (PCLSs) have emerged as a promising model system for chronic lung diseases (14). PCLSs are 300–500-μm-thick sections of lung tissue that can be generated from explanted or resected lung tissue (15). PCLSs model lung

structure and function in its native three-dimensional (3D) environment, thus reflecting natural interactions between cells, molecules, and the extracellular matrix (ECM) *ex vivo*. Subjecting healthy donor lungs to a fibrotic cocktail treatment (transforming growth factor-β, platelet-derived growth factor-AB, lysophosphatidic acid, and tumor necrosis factor-α) over a time course of 5–7 days results in an *ex vivo* model of pulmonary fibrosis initiation (16) that can be used to screen candidate interventions (17–20). To further develop PCLSs as a robust tool, standardization of PCLS generation and culture is needed. Studies altering the structure and microenvironment of the PCLS, using stretch or novel biomaterials to alter stiffness and matrix–cell communication, would be helpful to better mimic fibrotic disease. Techniques that allow genetic manipulation in human lung tissue would further maximize the use of PCLSs for mechanistic and therapeutic studies.

Hydrogel biomaterials can be engineered to control and study cell–matrix interactions in real time. Advances in lung decellularization techniques have fueled a growing interest in biomaterials from decellularized ECM. To study the influence of cell–matrix interactions on fibrotic cellular activation *in vitro*, a new class of photoaddressable hybrid hydrogels containing a dynamically tunable polyethylene glycol backbone and clickable decellularized ECM has been developed (21, 22). These materials support on-demand spatiotemporal control over local mechanical properties in 3D cultures facilitating epithelium–fibroblast interactions. Precisely designed microenvironments can facilitate controlled biological studies aimed at understanding the dynamic cell–matrix interactions that occur during fibrosis-related ECM remodeling (23). Current models may not fully recapitulate the *in vivo* ECM or the *in vivo* inflammatory milieu and lack an air–liquid interface.

Organoids are 3D structures that mimic the organ cellular and structural microenvironment and enable cell–cell interactions to be studied in a tissue-like environment. Lung organoids have been developed using a bead-based microscaffold lung cell coculture approach to generate a tissue-like structure for disease modeling and studying epithelial–mesenchymal interactions (24–27). Using combinations of primary and induced pluripotent stem cell (iPSC)-derived cell types and ECM, a 3D model was created with a phenotype resembling IPF. Progressive fibrosis was seen over time in culture, which correlated with increased senescent cells and a senescence-associated secretory phenotype. Such models could be scalable and amenable to high-throughput drug screening with newer 3D imaging techniques and machine learning algorithms. Current models lack vasculature and air flow. To study cell–cell interactions across multiple cell types, advances in model complexity are needed to enable the addition of cell types such as endothelial and immune cells.

Pluripotent Stem Cells

Methods for the generation of iPSCs from peripheral blood and the directed differentiation of iPSCs into a variety of lung epithelial lineages have been developed for disease modeling or cell-based therapies (28–31). Reprogramming patient-specific somatic cells can provide an inexhaustible source of disease-specific iPSCs for disease modeling, drug screens, or cell reconstitution. For example, by using patient-derived cells that carry a disease-causing mutation, *SFTPC*^{I73T}, known to be expressed solely in AT2 cells, mechanisms associated with the inception of type 2 alveolar epithelial cell dysfunction can be elucidated, including potential druggable target pathways for therapeutic intervention (32). To move from epithelium-only models of disease inception to more complex models of epithelial–mesenchymal crosstalk, models have been developed where iPSC-derived epithelium can be cultured together with mesenchymal lineages in 3D cultures (33). These models offer an opportunity for more complex studies of disease pathogenesis, including measures of fibrogenesis, the potential to employ CRISPR gene editing to examine the impact of specific polymorphisms or mutations, and the ability to screen for drugs that ameliorate either epithelial dysfunction or the fibrotic mesenchymal response. Important gaps to be addressed include the development of standardized differentiation procedures for all lung cell types and cocultures of multiple cell types to better mimic the *in vivo* cellular environment of interest.

Single-Cell Profiling

Single-cell profiling technologies offer unprecedented opportunities to profile DNA, mRNA, and proteins at a single-cell resolution (34). The application of single-cell RNA sequencing led to the recognition that reduced numbers of AT1 and AT2 cells and increased numbers of airway epithelial and systemic venous endothelial cells were hallmarks of human pulmonary fibrosis (35–38). Cell populations that were not described previously, such as the profibrotic macrophages (38, 39) or the aberrant basaloid cells, were identified (37, 40, 41). An atlas of IPF cell data has been publicly shared in a user-friendly data-sharing and dissemination portal (www.IPFCellAtlas.com) (42). However, limitations to single-cell data acquired to date include an overdependence on end-stage lung tissues and the lack of samples from a diverse patient population with various etiologies of pulmonary fibrosis.

Specific compartments such as pulmonary lymph nodes have not yet been studied and may be important to fully understand disease mechanisms and to better characterize the role of the immune system in pulmonary fibrosis. In addition to single-cell or nuclear or spatial transcriptomics, single-cell resolution metabolomics, genomics, and epigenomics should also be applied. Development of standards for data preservation and sharing are critically required to make the data widely accessible. With the emergence of these complex datasets, computational models of the human fibrotic lung could be used to simulate the effects of disease-modifying perturbations on fibrosis and potentially help in prioritizing drug targets and compounds.

Standardized collection of well-characterized samples stored in media or conditions that allow single-cell profiling across the spectrum of pulmonary fibrosis is vitally needed. Such well-characterized collection of cells and tissue would add great value for both single-cell profiling and use in other model systems discussed above. This endeavor should extend beyond lung explants to identify resources for lung tissue from patients with preclinical pulmonary fibrosis, familial pulmonary fibrosis, and non-IPF ILD to maximize impact. Clinically performed bronchoscopies and lung biopsies represent opportunities for sample collection, and the development of a live-cell bank was collectively identified as a resource to facilitate future mechanistic inquiry.

Translating Preclinical Fibrosis Models to Human Disease

The translation of preclinical models to human disease in pulmonary fibrosis

remains a "valley of death" in drug development (43). Modeling of lung fibrosis is a vastly complex task, and even the most robust translational system can only ever characterize a portion of the true disease biology (44). There is no perfect model (Table 1). Deriving translational value from preclinical modeling requires using models correctly and timing interventions appropriately (45). A small fraction of studies evaluating candidate IPF treatments in the bleomycin rodent model have tested the drugs as therapeutic and not as preventive agents (46). There is a lack of published preclinical data from disease models for most of the compounds tested in human studies during the last decade that eventually failed to demonstrate favorable results. The lack of access to the experimental details makes it impossible to understand the predictive value of the models for future clinical trial success. Publishing these results would have immense value to the scientific community.

There is an opportunity to have greater integration between diverse stakeholders to translate discoveries related to the pathobiology of pulmonary fibrosis into new drugs. There are several novel investigational therapies in the clinical development pipeline. It may be beneficial to foster discussion to promote incorporating the preclinical models discussed here for early testing of experimental compounds. Such a collaborative approach may help select which agents are more likely to succeed in clinical trials while helping us understand which, if any, of these newer models have high predictive value of demonstration of efficacy in humans.

Early Disease Risk Factors and Methods to Improve Diagnosis

IPF and other fibrotic ILDs develop insidiously over years. In most cases, a diagnosis of pulmonary fibrosis is made only after considerable disease progression has transpired. Early detection and consequently therapeutic intervention may provide opportunities to preserve lung function and improve overall survival. However, for this to occur, greater recognition of risk factors for pulmonary fibrosis, development of methods to enable early diagnosis, and validation of biomarkers for near-term disease course prediction are essential.

Interstitial Lung Abnormalities

Research over the past decade supports the presence of interstitial lung abnormalities (ILAs), which are incidentally detected interstitial changes on chest computed tomography (CT), as a risk factor for ILD (47–54). Individuals with ILAs share certain genetic risk factors with adults diagnosed with IPF and other fibrotic ILDs. For example, the *MUC5B* variant (rs35705950), short telomere length, and IPF-related rare genetic variants are linked with ILAs (50, 55, 56). The presence of ILAs is independently associated with a 1.3 - 2.7 hazard ratio for death (49). In a cohort of first-degree relatives of patients with familial pulmonary fibrosis, ILA progression occurred in 20% of participants, with half (10%) developing incident ILD over 5 years (57). In another familial cohort, worsening respiratory symptoms occurred in 40%, and worsening fibrosis measured by quantitative CT occurred in 33%, over 4 years (58). Despite a greater awareness of the potential clinical impact of and risk for ILA progression (53, 59), the drivers of progression from ILAs to clinically significant pulmonary fibrosis remain poorly understood. Important knowledge gaps remain, such as how to integrate demographic characteristics, radiologic patterns, and genetic information to identify individuals with the highest risk of near-term disease progression. Such knowledge is essential to enabling future therapeutic efforts focused on prevention of pulmonary fibrosis (60) and represents an important unaddressed opportunity with significant implications for individual risk prediction.

Common and Rare Genetic Variants

The past decade has seen considerable advances in our understanding of rare and common genetic variants associated with IPF (61–63). A *MUC5B* promoter variant is observed in over 30% of subjects with familial or sporadic IPF and can identify individuals at risk for preclinical pulmonary fibrosis (9, 50, 61). Up to two dozen common genetic variants have been shown to contribute to the risk of IPF (62, 64). Rare variants in genes related to surfactant processing and telomere/chromosomal biology have been implicated in familial pulmonary fibrosis and have also been observed in patients with "sporadic" IPF, although typically at somewhat lower prevalence than is seen in familial cohorts (65–69). These findings raise the possibility that a subset of sporadic IPF cases represent the "index" case in a family, but no studies to date have yet evaluated the impact of such variants on disease risk in the children of patients with IPF.

Major gaps remain in our understanding of genetic risk factors. How do common genetic variants and environmental risk factors contribute to the development, progression, and phenotypic heterogeneity of pulmonary fibrosis? How do rare and common genetic variants interact to mediate and modulate disease risk? What is the role of testing for genetic variants when assessing risk for pulmonary fibrosis in individuals with a family history of sporadic or familial pulmonary fibrosis, and how should results of genetic testing inform recommendations for screening for pulmonary fibrosis? There remains a missing heritability because common and rare variants do not completely explain the heritable risk for this disease. To date, genetic studies have focused on non-Hispanic White people. Greater representation of patients across ethnicities is crucial for a comprehensive elucidation of genetic drivers of pulmonary fibrosis.

Blood-based Biomarkers and Progressive Pulmonary Fibrosis

Multiple candidate blood-based biomarkers have been studied for disease course prediction in IPF. However, there remains no clinically used blood-based biomarker for individual disease course prediction in IPF. Although nearly all patients with IPF progress after diagnosis, variable proportions of those with non-IPF ILD develop a progressive fibrotic phenotype, termed "progressive pulmonary fibrosis" (PPF), with a survival that closely resembles IPF (70, 71). Currently, there is no ability to predict which individuals will develop PPF, and this represents a critical gap in knowledge with significant therapeutic implications. Criteria proposed to identify PPF consist of clinical features that often precede death or lung transplant, including categorical decline in FVC and D_{LCO}; increasing extent of fibrosis on high-resolution CT; worsening respiratory symptoms, including cough and dyspnea; and combinations of these features IPF (70, 71). These conventional measures of ILD progression are easily applied and have been used to successfully test the impact of therapeutic interventions on PPF (4). A PPF clinical practice guideline was recently published (70) that was met with considerable skepticism by the international

community. Criticism of these opinion-based criteria stemmed from their reliance on retrospective cohort data, heavy extrapolation from IPF, and arbitrarily assigned measurement periods (72–74). Recent studies have corroborated these concerns, finding that near-term FVC decline and long-term transplant-free survival were highly heterogeneous, depending on the PPF criterion satisfied (71, 75). The uncertainty regarding the optimal criteria or their timing jeopardizes impactful research and efficient clinical care. As such, ongoing research is needed to better understand this observed phenotypic heterogeneity and define PPF.

Composite models are limited in their ability to predict near-term disease progression (76), suggesting a better ability to identify advanced disease than biologically active disease. Because current criteria for PPF are based on functional and imaging criteria reflective of short-term disease progression (70), biomarkers with a greater predictive ability for near-term disease progression over longer-term survival are essential. Using an unbiased proteomic approach, 17 biomarkers were associated with near-term disease progression, defined as ⩾10% FVC decline, death, or transplant over 1 year, in both discovery and validation cohorts of participants with non-IPF ILD (77), suggesting that a multibiomarker panel may be needed for near-term disease prediction. Additional research to identify clinically actionable blood-based biomarkers or a combination of multimodal biomarkers remains an important unmet need to enable earlier therapeutic intervention for both IPF and non-IPF ILD. To facilitate data sharing, samples collected under sponsored research could be made available and centrally analyzed to identify and validate the performance of biomarkers across studies.

Radiomics and Emerging Imaging Technology

The past decade has seen increasing research into CT-based radiomics of pulmonary fibrosis. Image texture features from 3D CT datasets are converted to numerical values for mathematical analyses using advanced computational techniques. Single–time point radiomic scores, such as the CALIPER (Computer-Aided Lung Informatics for Pathology Evaluation and Ratings)-derived vessel-related structure scores, have been shown to predict survival in IPF (78). Short-term changes in radiomic scores have also been associated with survival; for example, an increase in quantitative lung fibrosis score ⩾4% over 6 months was associated with a reduced progression-free survival in IPF (79). Several radiomic scores, such as quantitative lung fibrosis and quantitative interstitial lung disease, have been used to detect treatment effect in recent IPF or systemic sclerosis–associated ILD clinical trials (80, 81).

Standardization of high-resolution CT acquisitions across study protocols and clinical centers is needed to enable various radiomic measurements to be compared across large numbers of individuals and ILD subtypes. Variations in CT acquisition (sequence parameters, radiation dose, inspiratory air volume) affect imaging outputs (82). The development of a large repository of CT datasets in combination with disease outcomes would facilitate validation of radiomic algorithms for disease course prediction for both established disease and at risk for disease populations. This information could be combined with other omics-based biomarkers for elucidation of pathobiology and development of individual risk prediction.

An imaging-based approach with potential utility for early microscopic diagnosis and disease monitoring over time is endobronchial optical coherence tomography (EB-OCT). EB-OCT is a bronchoscope-compatible, rapid imaging technology that provides microscopic resolution 200 times greater than CT in lung tissue volumes 100 times larger than surgical lung biopsy (83, 84) and exhibited 100% sensitivity and specificity for both histopathologic usual interstitial pneumonia and clinical IPF diagnoses in patients undergoing diagnostic surgical lung biopsy; there was high agreement between EB-OCT and histopathologic ILD pattern (85). Polarization-sensitive EB-OCT also detects birefringence and fiber orientation in organized tissues, such as collagen, and distinguished destructive fibrosis, nondestructive interstitial fibrosis, and normal parenchyma in participants with ILD (86).

The optimal imaging modalities to best detect early, clinically significant disease and how this information can be incorporated to better predict individual disease course remain to be determined. There was collective consensus on the need for ongoing development of tools to enhance early diagnosis and disease course prediction. It is likely that a multimodal strategy would be needed to best inform individual disease risk for clinical decision making (Figure 1). Such tools would be of great relevance not only to individuals with ILAs or with a family history of pulmonary fibrosis but also to those at risk of developing pulmonary fibrosis in the setting of autoimmune-related diseases such as systemic sclerosis and rheumatoid arthritis.

Machine Learning for IPF Risk Prediction

Emerging research highlights the potential utility of machine learning technology for secondary disease prevention. Delays in diagnosis and initial misdiagnosis are common in patients with IPF because of nonspecific symptoms that overlap with those of more common pulmonary diseases (87).

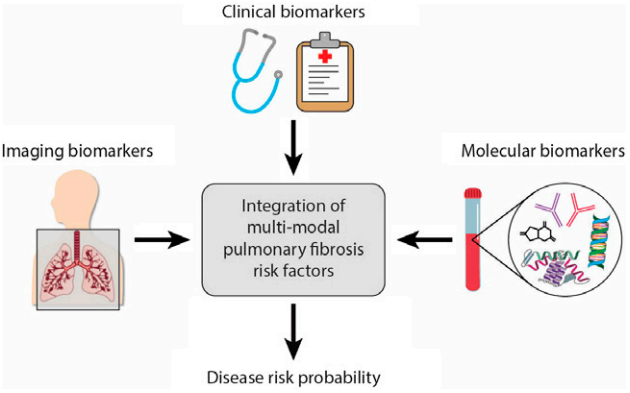

Figure 1. Integration of multimodal risk factors for disease risk probability. The schematic illustrates the integration of imaging, clinical, and molecular information to determine disease risk for an individual patient. Disease risk could pertain to the development of pulmonary fibrosis for those with interstitial lung abnormalities or a family history of pulmonary fibrosis or to the development of disease progression for those with established pulmonary fibrosis.

Using comorbidity signatures from the electronic health records of individuals with IPF, the zero-burden comorbidity risk score for IPF was developed as a screening tool for diagnosis of IPF (88). This machine learning algorithm leverages available data in the electronic health records. The zero-burden comorbidity risk score for IPF predicted IPF diagnosis up to 4 years in the future with good accuracy and, when applied 1 year before diagnosis, achieved positive likelihood ratios exceeding 30 at 99% specificity.

Innovative Approaches to Clinical Trial Design for Pulmonary Fibrosis

Traditional drug development pathways can take up to 10 years (double the median survival of IPF) to evaluate a single treatment. Favorable early-phase trial results are no guarantee of late-phase efficacy, with several late-phase trials recently discontinued because of lack of efficacy for IPF (e.g., the ISABELA [A Clinical Study to Test How Effective and Safe GLPG1690 Is for Subjects with IPF When Used Together with Standard of Care], STARSCAPE [A Study to Evaluate the Efficacy and Safety of Recombinant Human Pentraxin-2 (rhPTX-2; PRM-151) in Participants with Idiopathic Pulmonary Fibrosis], and ZEPHYRUS [Evaluation of Efficacy and Safety of Pamrevlumab in Participants with IPF] trials) (89). Use of background treatment with nintedanib or pirfenidone affects the potential magnitude of the treatment effect of new agents, and the feasibility of recruitment can be more difficult because of changing practice patterns and intense competition for participation of a limited number of patients.

Improving the Efficiency of Early-Phase Trial Design

There remains a need to improve the efficiency of not only late-phase but also early-phase trials. This would enable multiple candidate drugs to be tested in early-phase studies in a shorter time frame to identify the most promising ones to move to late-stage trials. One way to facilitate this is to maximize biomarker assessments to obtain pharmacodynamic information. Several proof-of-concept studies have been conducted that have incorporated assessment of target engagement of investigational therapies in participants with IPF. Reduction in alveolar macrophage expression of galectin-3 was detected using an inhaled galectin-3 inhibitor in a phase I/IIA study (90). Use of ^{18}F-fluorodeoxyglucose positron emission technology (PET) demonstrated a reduction in ^{18}F-fluorodeoxyglucose uptake in fibrotic lung regions, confirming metabolic effects of a phosphatidylinositol-3-kinase/mammalian target of rapamycin inhibitor in a phase I study (91). An $\alpha_v\beta_6$-specific PET probe confirmed target engagement of an inhaled inhibitor of $\alpha_v\beta_6$ integrin in a small study of eight participants (92). Other developments that may increase efficiency include Bayesian analysis, which incorporates prior control data into the current trial of interest (93).

Molecular imaging may provide important insight within clinical trials of pulmonary fibrosis, especially within early-phase trial design. A number of molecular probes have been developed for noninvasive assessment of fibrosis (94). PET probes targeting type I collagen and $\alpha_v\beta_6$ integrin and a fibroblast-activating protein inhibitor probe have been translated into use in humans with pulmonary fibrosis (95–99). In addition to enabling assessment of target expression and engagement, molecular imaging also could be used to assist with dose selection or early assessment of treatment response and provide a noninvasive means for a molecular-based cohort enrichment strategy (100). Blood-based biomarkers may also provide an early window into *in vivo* drug effects. Routine incorporation of biomarkers into early-phase trials can also serve to validate candidate biomarkers for identification of individual treatment response.

Innovations in Trial Design

Innovative concepts in trial design have been introduced for therapeutic development for pulmonary fibrosis. Pragmatic trials that increase the number of potential study participants and provide more generalizable results have been demonstrated to be feasible in IPF. CleanUp-IPF (Study of Clinical Efficacy of Antimicrobial Therapy Strategy Using Pragmatic Design in Idiopathic Pulmonary Fibrosis) used limited inclusion and exclusion criteria, completed enrollment ahead of schedule, and produced results similar to those of the EME-TIPAC (Treating Pulmonary Fibrosis with Co-trimoxazole) trial, a placebo-controlled traditional explanatory trial that also employed cotrimoxazole in participants with IPF (101, 102). The currently enrolling PRECISIONS (Prospective Treatment Efficacy in IPF Using Genotype for Nac Selection) study includes several pragmatic elements and represents the first pharmacogenetic trial in IPF while leveraging a partnership with the Pulmonary Fibrosis Foundation to facilitate recruitment and use of biospecimens through the Pulmonary Fibrosis Foundation Patient Registry (103).

Other forms of trial design, such as umbrella, basket, or platform trials, have been pioneered in oncology (104) and may hold promise for use for pulmonary fibrosis. Adaptive platform trials have been used for other chronic and rare diseases, such as amyotrophic lateral sclerosis (105). An adaptive platform trial allows the evaluation of multiple treatments within an integrated clinical trial infrastructure using a single main protocol and integrated statistical framework. Interventions may be administered in combination, with the list of available treatment arms changing over time as some are found to be effective, ineffective, or harmful and as new treatments become available (104, 106, 107). The ability of the platform trial design to address combination treatment strategies and heterogeneity of treatment benefit across subgroups makes this approach particularly relevant for the evaluation of interventions for pulmonary fibrosis. In addition, the stream of information acquired during the study period can trigger specific changes or adaptations in the trial structure in real time, such as altering randomization proportions or early termination of an arm or subpopulation for demonstration of efficacy, futility, or harm, according to prespecified decision rules (106). Fundamentally, this means that an adaptive platform trial can enable the most information on the therapies that are most effective and that, theoretically, outcomes for patients involved in the trial should improve over time.

Trial Endpoints and Statistical Considerations

Important progress in understanding the strengths and limitations of potential endpoints in late-phase trials in IPF has been made over the last decade. Approval of nintedanib and pirfenidone by regulatory agencies was based on efficacy for slowing the rate of FVC decline over 52 weeks of treatment (2, 3). Other studies have used composite endpoints, such as progression-

Table 1. Novel Models and Tools to Study Pulmonary Fibrosis

Model/Tool	Advantages	Limitations
Ferret model	Pathology recapitulates characteristic key features of pulmonary fibrosis, including persistent fibrosis, prominent MUC5B expression in distal airways, and aberrant repair	Cost and complexity of ferret model Lifespan 5–10 yr with onset of geriatric diseases between 3 and 4 yr Fewer ferret-specific reagents available to characterize the model Requires more compound for drug testing than mouse models Therapeutic applications not yet demonstrated
Sftpc mouse models	Develop spontaneous fibrosis Model early disease Elaborate cytokines and biomarkers detected in pulmonary fibrosis patients Can be used to benchmark drug efficacy	*Sftpc* locus unavailable for lineage tracing Does not model bronchiolization
Precision-cut lung slices	Natural composition of cells and ECM Live imaging of cell–cell and cell–ECM interaction *ex vivo* Early stages of fibrosis can be induced Can be used for drug discovery and validation	Limited culture time No ventilation/perfusion No homing of nonresident cells Limited value for translation in relation to route of administration of therapeutic agents (e.g., inhaled or systemic administration)
Hydrogel biomaterials	Enable manipulation of mechanical properties Biochemical changes can be decoupled from biophysical changes Can probe cell–matrix interactions Can create sex-specific models Many cell types can be included Can be used for drug discovery and validation	No air–liquid interface No cyclic stretch Current models may not capture the complexity of the *in vivo* ECM or *in vivo* inflammatory milieu
Lung organoids	Enable epithelial–mesenchymal cellular interactions to be studied High-throughput analysis possible for drug screening and biological readouts Many cell types can be included Mechanotransduction forces can be modeled	No vasculature or airflow Does not model bronchiolization Takes a reductionist approach; not all cellular and matrix components are present No homing of nonresident cells
Pluripotent stem cells	Inexhaustible source of cells for generating lung lineages of interest for disease modeling, drug screening, or cell-based therapies Patient-specific, editable, and scalable Allows production of initially normal patient-derived cells to replay or recapitulate disease onset/emergence *in vitro*	Lack of standardized differentiation procedures for all lung cell types Differentiation protocols for some relevant cell types (e.g., AT2 cells and lung mesenchymal lineages) are currently a work in progress Cocultures of multiple cell types needed to fully recapitulate *in vivo* environment
Single cell profiling	Allows discovery of novel cellular phenotypes and states associated with fibrosis Provides a detailed atlas of molecular changes and cellular interactions that occur in lung fibrosis Information obtained can be used to orient therapy development focused on specific cell populations in the fibrotic lung	Dependent on tissue availability Only captures transcriptional regulation, not post-transcriptional effects (e.g., mRNA stability or post-translational modifications) Most results to date have been from end-stage lung tissue and are limited in ethnic, racial, and geographical representation

Definition of abbreviation: ECM = extracellular matrix.

free survival, commonly defined as a composite of decline in FVC or death, as a primary endpoint in IPF studies (108, 109). However, composite endpoints often use different components and thresholds, making cross-study comparisons difficult. Discordant effects of a drug on various components of a composite endpoint can obscure efficacy, and a less important component can drive treatment differences, dominating the analysis and interpretation. Although clinically meaningful, the development of acute exacerbations of IPF as an endpoint is better suited as a secondary endpoint than as a primary endpoint because of the large sample size needed to demonstrate a significant treatment effect for decreasing the frequency of acute exacerbations of IPF. Mortality as a primary endpoint has the highest clinical relevance and meaning to patients; however, a mortality primary endpoint often requires a larger sample size and prolonged trial duration, limiting overall feasibility (110, 111).

Statistical considerations in endpoint selection include improving the inherent information available in an endpoint (e.g., survival [time to event] instead of mortality [binary], recurrent events instead of time to first event) and the relevance of an endpoint (e.g., hierarchical composite endpoint [win ratio] instead of time to first component of a composite endpoint) (112, 113). Exploring home-based functional measures (e.g., home spirometry) may provide more repeated measures, and the potential loss in precision

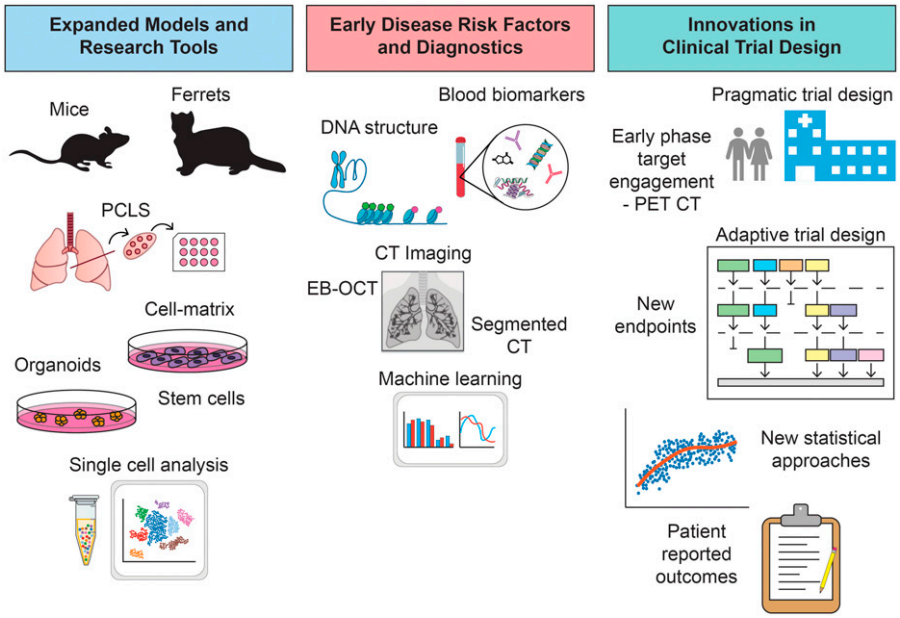

Figure 2. Tools, diagnostics, and innovations to advance discovery, diagnosis, and drug development for pulmonary fibrosis. CT = computed tomography; EB-OCT = endobronchial optical coherence tomography; PCLS = precision-cut lung slices; PET = positron emission tomography.

relative to clinic-based measures may be counterbalanced by increased repeated measures and less dropout (114). However, this approach remains an active research area. The application of more sophisticated statistical methods can also lead to new insights for endpoint selection. Machine and statistical learning methods can be used to assist with biomarker discovery through data-driven subgroup identification (115). Novel data integration methods allow better prediction capabilities of biomarkers by borrowing information from internal auxiliary data (116–118) or by incorporating external information from other studies (119–122). These methods work for both cross-sectional and longitudinal analyses, boosting statistical power while accounting for the study population heterogeneity. Increased incorporation of biomarker discovery into clinical trials and sharing of individual-level data from trials, registries, and cohort studies will allow more patient-level meta-analyses and data integration opportunities to inform subsequent clinical trial design.

Patients living with pulmonary fibrosis experience complex and interrelated symptoms of dyspnea, cough, anxiety, and depression that affect quality of life. Patient-reported outcome (PRO) measures enable assessment of patient symptoms and quality of life (123). PROs validated for use in IPF and ILD include the King's Brief Interstitial Lung Disease Questionnaire, the Living with Idiopathic Pulmonary Fibrosis questionnaire, and the Fatigue Severity Scale (124–126). Including PROs in the management of patients with IPF and in clinical trials evaluating the utility of new pharmacotherapies adds a critical, patient-centered dimension to efficacy assessment in clinical trials. Further development, validation, and inclusion of PROs as a measure within clinical trials is needed to strengthen inclusion of patient

Table 2. Research Opportunities for Advancing Pulmonary Fibrosis

Novel models and research tools to better study pulmonary fibrosis and uncover new therapies
- Develop models that recapitulate the evolution from injury through fibrogenesis to resolution
- Test drug candidates in the established fibrotic phase of disease
- Expand collection of live cells at the time of routine clinical procedures (i.e., bronchoscopy)
- Develop a live-cell bank to examine different mutations or gene variants as they relate to disease pathogenesis
- Standardize protocols for tissue and sample collection to yield samples from multiple fibrotic lung diseases at various clinical stages
- Develop a central repository for single-cell analyses of tissue and models

Early disease factors and methods to improve diagnosis
- Determine risk factors and mechanistic drivers of disease progression from preclinical disease to pulmonary fibrosis
- Develop tools to predict individual risk for progressive pulmonary fibrosis in non–idiopathic pulmonary fibrosis interstitial lung disease
- Increase representation across ethnicities for elucidation of genetic risk factors for pulmonary fibrosis
- Determine optimal strategies for screening/surveillance in high-risk populations for pulmonary fibrosis (familial pulmonary fibrosis families, connective tissue disease)
- Define recommendations for incorporating genetic testing into clinical practice for individuals with established pulmonary fibrosis
- Standardize high-resolution computed tomography acquisition parameters to facilitate large-scale radiomic analyses
- Develop tools to enhance early diagnosis and disease course prediction

Innovative approaches to clinical trial design for pulmonary fibrosis
- Incorporate novel imaging and blood-based biomarkers into early-phase clinical trials
- Leverage innovative statistical methods to enable adaptive trial design
- Develop a trial platform to assess multiple candidate therapies for pulmonary fibrosis across a range of subtypes of pulmonary fibrosis
- Synergize trial design to facilitate data sharing and cross-validation of clinical trial results
- Increase diversity and inclusion in recruitment and enrollment of patients with pulmonary fibrosis into clinical trials
- Develop and validate clinical trial endpoints to support the conduct of adequate and well-controlled studies

experience and quality of life as essential components of treatment efficacy.

Summary

Although great progress has been made over the past decade, there remains much work to be done to improve the lives of patients living with pulmonary fibrosis. This summit provided a platform for investigators, sponsors, physicians, and patients to share innovative ideas with the pulmonary fibrosis community with the goal of ultimately improving outcomes for patients with pulmonary fibrosis (Figure 2). It is our hope that the collective research needs put forth (Table 2) will catalyze collaboration and discoveries that will one day make curing pulmonary fibrosis a reality. ■

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