Open-Access Biorepository for Idiopathic Pulmonary Fibrosis

The Way Forward

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Abstract

Although widespread use of animal modeling has transformed pulmonary research, the overarching goal of biomedical research is to enhance our understanding of human physiology and pathology. Thus, we believe that future gains in understanding human lung disease will be enhanced when studying patient-derived samples becomes an integral part of the investigational process. For idiopathic pulmonary fibrosis (IPF), investigators need quality human specimens, collected in a standardized fashion, along with carefully annotated, long-term clinical and outcomes data to address current knowledge gaps. Access to human lung tissues through commercial entities or the Lung Tissue Resource Consortium, an NHLBI-funded consortium, has demonstrated the feasibility of this approach. However, these samples are not always well annotated or collected uniformly and are limited in their breadth to address future IPF research needs. Therefore, we propose leveraging ongoing and future studies in IPF to establish a biorepository that will meet current and future needs of IPF investigations. Specifically, we propose that blood, cell, and lung samples, linked to robust longitudinal clinical phenotyping generated from future industry, federally sponsored, and investigator-initiated clinical studies be prospectively and uniformly collected and stored in a biorepository and linked registry. Here we outline standardized methodologies that would allow specimens and clinical data collected from different studies to be integrated and accessible to the IPF research community for investigations that will inform future basic and translational research in IPF. Such a biorepository needs the combined efforts of all stakeholders, to be driven by projected future scientific needs and to be available to all qualified researchers. We believe this infrastructure is crucial, is feasible, and would accelerate research in IPF.

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Pulmonary physicians and scientists, pharmaceutical industry investigators, patient advocacy groups, and federal health agencies (e.g., National Institutes of Health [NIH]) all strive to better understand lung disease in the hopes of developing strategies capable of alleviating suffering and improving quality of life. Investigative efforts to accomplish this goal take many forms, including bench-based investigation, translational studies, and clinical trials. Through such efforts over the past decades we have gained greater awareness of the pathophysiology of numerous lung diseases. For example, pronounced strides in our understanding of cystic fibrosis (CF) through identification of CFTR mutations; consideration of how the mutation affects folding, localization, and function of the protein; and correction of the functional defect have led to new treatments for

patients with CF in the past few years (1). Insight into other pulmonary diseases has similarly grown; in idiopathic pulmonary fibrosis (IPF), we have recently witnessed the emergence of pirfenidone and nintedanib as new potential therapies in IPF (2, 3).

The direct study of patient data and tissues is central to accelerate progress in understanding the pathobiology of human disease. In the case of rare diseases such as IPF, studying patient data and tissue samples is hampered by the lack of well-phenotyped, well-processed, and clinically annotated samples, although some institutions have embarked on this approach (4). Formal collaborations among investigators who pool samples and data may result in adequate sample sizes to assess biologic differences or drug effects between the diseased and healthy states and is one solution to this limitation. Making the most use of data and samples, though, requires that all samples be collected and stored in a uniform way and that the same data be obtained from each subject. We believe the most efficient and effective way to overcome this limitation is with a standardized, centralized human tissue biorepository.

The successful development of a central biorepository that collects, phenotypes, and stores samples and linked clinical data for distribution to investigators throughout the IPF scientific community would be widely accessed, while enhancing "bedside-to-bench" research endeavors, improving our understanding of disease pathobiology, and increasing the likelihood of identifying potential therapeutic targets. Ultimately, this effort could facilitate cohort enrichment and endpoint selection for clinical trial design to allow for more efficient and effective trial readouts. Predicting disease progression and responsiveness to putative therapies and identifying potential therapeutic targets could all be improved through the use of a high-quality and comprehensive biorepository of IPF samples with linked clinical data.

We believe successful creation of this type of core resource requires that key stakeholders act as true partners, being involved in all aspects of planning and development where expertise exists. In this manuscript, investigators from academia and industry, and representatives from patient advocacy groups, highlight steps we are taking toward the creation of such a biorepository for IPF research and provide guidelines for the acquisition and storage of biologic specimens and clinical data.

Planning a Biorepository

Beginning in November 2012, the IPF scientific community held several meetings sponsored by the NHLBI (NHLBI Strategic Workshop on Future Directions in Lung Fibrosis Research, Bethesda, MD, November 2012) and the Pulmonary Fibrosis Foundation and the American Thoracic Society (Respiratory Cell and Molecular Biology Working Group on Lung Fibrosis Biologic Sample Planning Meeting, Philadelphia, PA, May 2013) to discuss the current state of IPF scientific research. Each meeting was attended by representatives from academia, industry, patient advocacy groups, and the NHLBI with the purpose of identifying gaps in knowledge, limitations of current approaches to biologic sample acquisition, and possible solutions to foreseen obstacles. A manuscript detailing scientific knowledge gaps in IPF arising from one of these meetings has recently been published (5). Among the recommendations in this document was the call for developing or enhancing an open-access biorepository of patient-derived samples (5).

With respect to biorepository development, we recognize that there are likely thousands of biological samples (with accompanying clinical information) that have been collected during prior industry- and investigator-sponsored clinical trials in IPF that are not efficiently used to advance discovery; many more will be collected in current and future trials. Existing samples that have been collected and stored in a variety of ways and with varying clinical information can still be useful to investigators wishing to undertake hypothesis-generating experiments or to test hypotheses in a small sample of subjects with IPF, and these samples should be made available to investigators for such purposes. We also recognize that, to protect proprietary information and intellectual property, only samples obtained from subjects receiving placebo in an industry-sponsored clinical trial are likely to be made part of an "open-source" biorepository; however, industry should consider depositing samples from patients receiving active compounds into the biorepository, at an appropriate time, to improve our ability to understand which patients may most benefit from specific therapeutic agents. Investigators conducting foundation- and federally sponsored studies should consider providing samples and clinical data as well. There has been general agreement from meeting attendees on these points.

Going forward, we propose that investigators consider leveraging the power of future federally, industry-, and foundation-sponsored clinical studies by prospectively collecting biologic samples in a standardized fashion from well-characterized study participants from whom adequate longitudinal clinical data are collected to address gaps in our knowledge of IPF. Clearly, such an endeavor will require the investment of financial resources, infrastructure, and personnel. Initial investments from key stakeholders (industry, federal agencies, individual investigators, and patient advocacy groups) will be necessary to implement a biorepository. Defraying the cost of ongoing expenditures related to sample upkeep and storage supplies may be achieved by collecting nominal fees from investigators seeking to use samples for research projects (as is commonly done in commercial enterprises).

The Informed Consent Process

During our discussions, it became clear that permissions sought when obtaining informed consent vary among investigations. Some, but not all, studies include "opt-in" sections for surplus biologic specimens (e.g., plasma, genetic material) to be stored indefinitely for future studies or for hypothesis generation. We believe these permissions as well as permissions to couple anonymized relevant clinical data with these samples will enhance the value of the biorepository by having samples available to investigate new ideas. Of course, with this permission comes great responsibilities; in a time when technology allows for sequencing of genomes and identification of individuals based on genetic profiling, there must be strict adherence to policies designed to protect human subjects from inadvertent or purposeful release of private health information. We strongly advocate that samples already in existence not be used for DNA profiling or genome sequencing unless specific consent was granted; however, for some studies (e.g., metabolomic profiling), retroactive local institutional review board approval should

be sought if necessary. For future trials involving patients with IPF, we recommend that wording encompassing the consent to store and use surplus materials for "big data" research, for sharing samples among investigators, and for potentially collecting clinical information beyond the end of the study protocol (e.g., vital status, further disease progression, response to therapy) be included in informed consent documents to take advantage of these precious biological specimens. Because samples to be collected necessarily will come from subjects potentially enrolled in or contemplating enrollment in clinical trials, study subjects should be given the option to participate in the biorepository concomitant with interventional or observational trials.

Biological Specimen Standardization

The recent NHLBI Workshop Report made specific recommendations that will undoubtedly enhance our understanding of IPF (5). Among these were the recommendations to standardize the methods of collection and distribution of human cell types relevant to IPF, to use "omic" approaches to better characterize novel pathways that influence IPF development, and to develop and validate biomarkers (5). Biologic samples under consideration for these studies include peripheral blood, although surgically obtained lung samples, bronchoscopic brushings and cryobiopsies, and bronchoalveolar lavage (BAL) will likely also be informative in this population. Although there are many acceptable ways to collect and store biologic specimens, standardizing the manner and timing of obtaining specimens from patients with IPF is the only way samples collected at different sites and at different times can be truly compared scientifically. An open dialogue among all interested stakeholders to address processing and identify the minimum amount and types of samples should be undertaken. Given the preponderance of studies that collect peripheral blood, we believe simultaneous collection of serum, plasma, and buffy coat cells is essential to the development of a biorepository, with specific attention to the collection and storage of viable cells that allow sophisticated experimental modeling. For studies that obtain lung tissue, frozen and formalin-fixed histologic sections, fibroblast cultures, alveolar epithelial cultures, extracellular matrix, and potentially fresh tissue for living lung slice cultures or other specific cell isolations are all valuable. For bronchoscopic studies, cell-free BAL fluid, bronchoscopic brushings for airway epithelium, and BAL cell pellets should be obtained (Table 1). The increased use of cryobiopsies through bronchoscopic procedures will likely also enhance sample collection. Clinical laboratory results obtained as part of study protocols should also be collected concomitantly. All samples should be collected using standard operating procedures and protocols that are integrated into the operations of each site collecting the samples. Such processes must take into account plans to aliquot samples into usable volumes, freezing samples at uniform temperature based on experimental needs, and storing samples at appropriate temperatures for long-term use. All samples should be coded with identifier labels including sample type, volume, and the date the sample was obtained and processed, which is critical to allow for linking of the sample to longitudinal clinical information. When samples are to be shipped to a centralized laboratory for cataloging, keeping inventory, and distribution, we recommend standardizing packing and shipping protocols. All protocols should be posted on a publicly accessible website.

Standardization of the timing of sample collection is also crucial. Patients with IPF are typically evaluated by a pulmonologist every 4 to 6 months. We recommend that biological specimens collected during clinical trials be obtained at least at this frequency as well for purposes of tracking longitudinal changes in cells, fluids, and tissues. This time point will correlate with longitudinal clinical information, which is often collected at 4- to 6-month intervals during clinical trials. If clinical information will be collected more frequently, biological samples should be obtained as reasonably possible at the same time for purposes of comparison. Finally, to help many participating partners to collect samples and clinical data uniformly, a website containing the detailed protocols should be established as noted above.

Acute exacerbations of IPF (AE-IPF) are defined as an acute, clinically significant decline in lung function of unclear cause (6) and may represent overlying superinfection with an unidentifiable organism or acute worsening of disease. Because of their poor prognostic implications, AE-IPF are often considered an endpoint in clinical trials as evidence of disease progression. Thus, biological samples, including blood and BAL (when available), should be collected from patients with IPF experiencing AE-IPF within the context of a clinical trial.

Longitudinal Clinical Data

To better assess the natural history of IPF, patients should be evaluated in a standardized manner at regular intervals, including standardizing methods of image acquisition. Clinical data that are collected will be aided immensely by the creation of patient registries, several of which are currently under development. Ideally managed by an independent Data Coordinating Center, these multicenter registries should collect baseline and longitudinal information, including demographics, histologic diagnosis, selected comorbidities, current and prior medications, environmental exposure histories, pulmonary function studies,

Table 1. Recommended biological specimens to be obtained from patients with idiopathic pulmonary fibrosis enrolled in clinical trials

Biological Compartment	Samples Collected
Peripheral blood	Serum, plasma, buffy coat cells, whole blood
Bronchoalveolar space	Cell-free BAL fluid, BAL cell pellet, airway brushing
Lung tissue	Frozen and formalin-fixed histologic sections, fibroblast cultures, alveolar epithelial cell cultures, cryobiopsies, extracellular matrix

Definition of abbreviation: BAL = bronchoalveolar lavage.

quality-of-life measures, and radiographic (i.e., high-resolution computed tomography [CT] scan) information. Data should be stored electronically and archived for future analyses to address novel hypotheses. Date of transplantation (when applicable) and vital status should also be recorded. Centralized storage of high-resolution CT images within the registry would allow researchers to address specific scientific questions, such as whether CT scoring of features of interstitial lung disease (e.g., ground-glass opacities, honeycombing, reticular abnormalities [7]) correlates with clinical and biomarker outcomes.

We believe that combining ongoing registries that are already collecting detailed baseline and longitudinal data on patients with a sample biorepository is likely to be the most economic and efficient use of investigator and patient time and resources. However, for such clinical information to be of maximum use, data from multiple centers need to be integrated seamlessly. This may require use of open-source software that all involved centers can agree on or universal adoption of a commercial platform. Certainly, rigorous attention to standardization of data collection, image acquisition, and storage practices paralleling those of biological samples as described above is necessary to ensure comprehensive data from each contributing investigator/institution. For valid and reproducible comparisons to be made among subjects from the various depositors in the most accurate and meaningful way, strict attention to these details is paramount. In so doing, this clinical data biorepository will be an invaluable tool to advance our understanding of IPF.

Managing a Biorepository

A biorepository of this magnitude could be created in stepwise fashion. At the outset, a "virtual biorepository" of known samples housed at the originating organization could be developed and annotated by a group of stakeholders. In subsequent steps, the biorepository could become more centralized and integrated, with an "honest broker" being charged with managing (storing, curating, and distributing) samples and clinical data. Ultimately, this type of infrastructure is necessary to ensure equitable access to samples. The IPF community has a vested interest in supporting this type of endeavor, both conceptually and financially, and we should consider this type of investment as critical to advancing IPF research by creating a national resource. The location of and degree of support for such a biorepository could be decided by funders and other stakeholders through a competitive grant process. Posting of available resources on a dedicated website will inform the IPF community of the availability of samples and data. A formal and standardized application process to request and obtain samples should include the justification of the number and type of biologic samples and the clinical data needed.

Recognizing that this type of biorepository would be considered open-access, governance and administration of the data and samples is of the utmost importance. Procedures for equitable access to data and samples (e.g., a study section composed of an independent panel of academic, industry, and/or federal representatives) would need to be outlined and applied fairly, based on scientific merit. Requests for access to protected health information must be scrutinized to ensure scientific necessity and would need to be overseen by local institutional review boards. Contributing stakeholders would need to agree in principle that samples and data provided to the biorepository become the property of the scientific community. Therefore, legal rights and academic credit for data generated from biorepository samples and clinical data would belong to the discovering investigator and would be addressed through Material Transfer Agreements and other processes as agreed on by all stakeholders.

Our proposed approach to biorepository development in IPF has been successfully initiated in the chronic obstructive pulmonary disease arena with the resulting development of a chronic obstructive pulmonary disease biomarker consortium, a model of academic, NIH, advocacy, industry, and U.S. Food and Drug Administration collaboration (8). A biomarker consortium in the IPF arena would be welcome and would certainly enhance collaborative efforts to identify and implement biomarkers in IPF.

Timeline

The theoretical framework of an open-access biorepository for IPF samples and data is described herein. Moving forward, it is necessary that interested stakeholders convene for purposes of detailing biologic specimen and data procurement standardization practices, discussing logistics of storing samples and data, identifying initial investment resources, and negotiating legal aspects of biorepository governance. These meetings could occur in conjunction with established conferences (such as the American Thoracic Society International Conference) or as part of a stand-alone meeting (such as an NIH Workshop or other meeting). To avoid unnecessary delays, we suggest that scientific protocols build on the cumulative experience of multiple existing biorepositories, with mechanisms to update and modify collection instated from initiation. Similarly, development should occur contemporaneously with emerging patient registries; thus, now is the time to redouble efforts in creating a biorepository. To ensure the needs of the IPF research community are being met, periodic reevaluation of practices and protocols should occur after biorepository development; this will make certain the biorepository functions as planned and incorporates the latest technologies and changes in patient care strategies.

Summary

We believe that IPF research will be substantially enhanced through the development of an open-source biorepository consisting of biologic samples linked to a registry of longitudinal clinical data obtained in a standardized fashion. With the emergence of clinical registries and as the number of IPF clinical trials and observational studies increases, we have an unprecedented opportunity for academia, industry, patient advocacy, and government to work together to create such a resource that will benefit IPF translational research in the years ahead. There is clear interest from all involved stakeholders and a defined need for this type of resource. More discussion regarding specifics of protocols and methods needs to occur, but we believe this type of biorepository is the way forward in IPF research. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

References

1 Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Dřevínek P, Griese M, McKone EF, Wainwright CE, Konstan MW, *et al*.; VX08-770-102 Study Group. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *N Engl J Med* 2011;365:1663–1672.

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 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.

4 Schwiebert LM, Estell K, Meadows T, Thannickal VJ, Rowe S, Sorscher EJ, Harris WT, Gaggar A, Dransfield M, de Andrade JA. Development and maintenance of a biospecimen repository for clinical samples derived from pulmonary patients. *Clin Transl Sci* 2014;7:336–341.

5 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.

6 Collard HR, Moore BB, Flaherty KR, Brown KK, Kaner RJ, King TE Jr, Lasky JA, Loyd JE, Noth I, Olman MA, *et al*.; Idiopathic Pulmonary Fibrosis Clinical Research Network Investigators. Acute exacerbations of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2007;176: 636–643.

7 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.

8 Casaburi R, Celli B, Crapo J, Criner G, Croxton T, Gaw A, Jones P, Kline-Leidy N, Lomas DA, Merrill D, *et al*. The COPD Biomarker Qualification Consortium (CBQC). *COPD* 2013;10:367–377.