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An Official American Thoracic Society Workshop Report: Translational Research in Rare Respiratory Diseases

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Abstract

Rare respiratory diseases (RRDs) are a heterogeneous group of disorders that collectively represent a significant health care burden. In recent years, strong advocacy and policy initiatives have led to advances in the implementation of research and clinical care for rare diseases. The development of specialized centers and research networks has facilitated support for affected individuals as well as emerging programs in basic, translational, and clinical research. In selected RRDs, subsequent gains in knowledge have informed the development of targeted therapies and effective diagnostic tests, but many gaps persist. There was therefore a desire to identify the elements contributing to an effective translational research program in RRDs. To this end, a workshop was convened in October 2015 with a focus on the implementation of effective transnational research networks and collaborations aimed at developing novel diagnostic and therapeutic tools. Key elements included an emphasis on molecular pathogenesis, the continuing engagement of patient advocacy groups and policy makers, the effective use of preclinical models in the translational research pipeline, and the detailed phenotyping of patient cohorts. During the course of the workshop, current logistical and knowledge gaps were identified, and new solutions or opportunities were highlighted.

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Contents

Rare or orphan diseases are defined as those with a prevalence of less than 1 in 2,000, or less than 200,000 cases in the United States. When combined, they affect approximately 5 to 8% of the population, but these disorders have been underrepresented in the spectrum of health care services delivery, as well as in the distribution of resources for clinical and translational research. Rare respiratory diseases (RRDs) make up an important subset (1, 2), and respiratory manifestations have a significant impact on patients' quality of life, function, and mortality. Although prevalence estimates vary widely, RRDs are estimated to affect up to 3 million persons in each of Europe and the United States (3). Recent reviews and statements (3–5) have identified gaps in the implementation of effective research and care delivery for patients with RRDs. The discovery and evaluation of biological tools for clinical use (i.e., translational research) were identified as priorities. To accelerate advances in the field, there was a perceived need to formalize the approach to effective translational research infrastructures and methodologies in RRDs, using selected RRDs as illustrative examples. The purpose of this document is to summarize discussion from a workshop convened in October 2015 at which the optimization of translational research in RRDs was addressed, in addition to current gaps and emerging opportunities.

Methods

An RRD workshop was held in Montreal, Quebec, Canada, on October 22–23, 2015. The goal was to build upon existing knowledge based on RRD research and provide consensus on its optimal organization and required infrastructure. The planning group and workshop were chaired by A.S.K., B.J.P., and Q.H. Workshop participants were chosen for their leadership roles in existing RRD research networks and programs, and they included representatives of patient advisory groups and local networks, patients with RRDs, clinician scientists, respiratory therapists, nurses, researchers, and trainees. Speakers were responsible for reviewing emerging infrastructures, methodologies, and areas of need in facilitating translational research in RRDs. Each workshop speaker contributed to the writing of this article. The workshop consisted of individual sections that covered five research-driven themes. All planning committee members and presenters completed a Declaration of Potential Conflict of Interest Form prior to the workshop.

Section 1: The Organization of Translational Research in RRDs

The goal of translational research is to exploit knowledge gained from experimental or clinical models to develop new diagnostics or therapeutics for patients

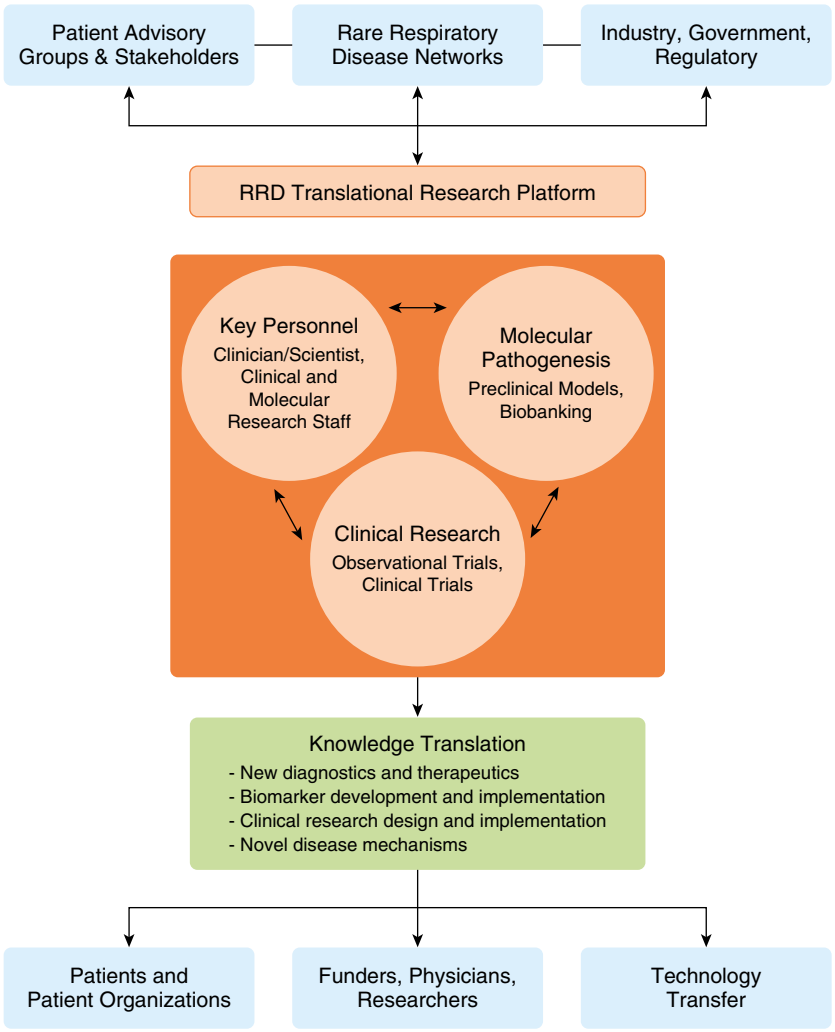

Figure 1. Optimizing translational research platforms for rare respiratory diseases (RRDs). Effective translational research on RRDs requires an integrated infrastructure that interfaces with critical stakeholders. Patient advisory groups and referral centers form a critical entry point and represent end users in the research pipeline (*blue*). The development of patient cohorts and recruitment into observational studies or clinical trials is facilitated by dedicated centers that participate in organized networks (*orange*). Key personnel (i.e., clinician scientists, clinical research coordinator/nurse, core experts in molecular pathophysiology) manage complex, multisystem chronic diseases, sample and data collection and analysis, as well as communicate with stakeholders and network partners. Understanding of disease pathogenesis is crucial, and the research exploits preclinical models, access to biobanks and registries, detailed clinical and phenotypic analysis in observational studies, and incorporation of diagnostic and prognostic biomarkers. Obstacles in RRD trial design include small sample sizes, chronicity, and limited effects over time. Emerging techniques include adaptive designs, N-of-1 and crossover trials, the incorporation of diagnostic or prognostic biomarkers, and clinical surrogate markers (e.g., the use of baseline decline in lung function prior to the intervention).

(6) (Figure 1). Traditional therapeutic development pathways are focused on screening-based technologies to identify new compounds and biomarkers and to target large populations for phase III clinical trials and postmarketing analysis. Although these populations are small for RRDs, the genetic or molecular defect is often known and can be exploited to define accessible therapeutic targets. This also permits the parallel development of biomarkers that serve as strong surrogate outcome variables in clinical trials. For instance, studies in model organisms to elucidate the role of the mechanistic target of rapamycin (mTOR) in the control of cell growth (7) complemented the interrogation of patient-derived biopsy samples for aberrant mTOR signaling and its role in the pathogenesis of lymphangioleiomyomatosis (LAM) (8). Within 10 years, a phase III clinical trial demonstrated the efficacy of the mTOR inhibitor rapamycin (sirolimus) in improving lung function and quality of life for patients with LAM (9, 10), and it helped establish clinical guidelines for the medical community (11, 12). In pulmonary alveolar proteinosis, studies on granulocyte-macrophage colony-stimulating factor signaling in isolated macrophages informed the characterization of granulocyte-macrophage colony-stimulating factor deficiency in patients and led to the development of diagnostic bioassays and replacement therapies (13). Similarly, studies on the genetic and molecular bases of cystic fibrosis (CF) have identified molecular targets for cystic fibrosis transmembrane conductance regulator (CFTR) corrector or potentiator therapies (14, 15).

RRD advocates have implemented innovative policy initiatives and research infrastructures to address the shortfalls in available clinical tools. One key step was the incorporation of all rare diseases under umbrella organizations that represent common clinical and research needs. In the United States, the National Institutes of Health Office of Rare Diseases was established in 1993, in part because of efforts by the National Organization for Rare Disorders advocacy group. The Rare Diseases Clinical Research Network (251 institutions worldwide and >200 rare diseases) was established to create disease-specific consortia; cost-sharing arrangements for research infrastructures; uniform data acquisition protocols; and an umbrella organization for disease registries, cohort studies, and randomized controlled trials. Additional missions include the direct engagement of patients and their advocates, as well as the training of new investigators. As a platform, the network facilitates clinical and translational research by establishing standard operating procedures for data collection, coordinating patient recruitment for large-scale studies, and providing a data management and coordinating center that supports study design and data analysis.

The Rare Lung Diseases Consortium is a subset of the Rare Diseases Clinical Research Network that collaborates with patient advocacy groups and supports the inclusion of those with no existing advocacy vehicle. The National Center for Advancing Translational Sciences was established to support the preclinical and clinical development of drugs and diagnostics for rare diseases. Similar advocacy organizations operate globally, including those represented at the workshop (*see* Table E1 in the online supplement). Moreover, a formalized, consortium-based approach to translational research in rare diseases of pediatric onset has been successfully implemented (16). Therefore, rare disease research networks, in collaboration with patient advocacy groups and policy makers, serve as critical drivers and coordinators of clinical and translational research.

Section 2: Advances in Clinical Infrastructure for Translational Research in RRDs

Successful clinical and translational research platforms for RRDs benefit from network-based recruitment of patients into prospective and longitudinal cohort studies that ideally encompass the pediatric-to-adult spectrum. The collection and analysis of granular (i.e., detailed) datasets allows for precise phenotyping, which supports research on basic disease mechanisms and the design of clinical trials by developing robust surrogate physiological or molecular outcomes (i.e., biomarkers). The elements of the translational research backbone discussed are described in the subsections below.

Registries and natural history studies

Registries are data collection systems suited for tracking outcomes in chronic diseases that can be accurately defined and rely on voluntary provision of secondary patient data from multiple centers to central repositories. Estimates of disease prevalence, practice patterns, and health care use can be inferred. However, the accuracy, homogeneity, and timeliness of clinical data cannot be guaranteed, and coordination for banking of biological samples is challenging. Natural history studies can be designed to collect a highly granular clinical and biological dataset over time. The quality and consistency of the data are optimized by centralization of protocols, banking repositories, and consistent measurement and analytic techniques. Genetic and molecular determinants can be tracked over time and correlated with clinical outcomes. Given the relative homogeneity of the patient populations, the collection of multiple data parameters over time can reduce bias and permit inference from retrospective analyses.

For instance, a National Institutes of Health–funded registry and natural history study were initiated in parallel. Registry data described the clinical spectrum of LAM (17). The NHLBI LAM natural history study was designed to frequently assess the evolution of disease and included the collection of biological samples that could be linked to clinical data. As a result, mTOR, along with multiple other putative therapeutic targets, was validated as an important disease modifier (18). Isolation of circulating tumor cells revealed that the abnormal cells in LAM exhibit metastatic properties (19). A number of biomarkers were identified in the blood (e.g., vascular endothelial growth factor-D [VEGF-D]) (20) and correlated with surrogate physiological or radiological outcomes. Detailed clinical and molecular phenotyping identified subsets of patients with differences in prognosis (e.g., rate of decline in FEV_1) or response to treatment (e.g., VEGF-D), which can inform the interpretation and design of translational or clinical studies.

Longitudinal cohorts that encompass the pediatric-to-adult spectrum

Because most rare diseases begin in childhood, the identification of early determinants of disease progression and developmental trends in longitudinal cohorts using adaptable study designs is desirable. Potential challenges include their long duration and expense, subject attrition, and requirement for large sample sizes. Attrition can be especially problematic during the transition from pediatric to adult care. However, these are often minimized in RRD research by the availability of

molecular testing and biomarkers, as well as the involvement of patient advisory groups in research networks. Illustrative successes and gaps were discussed for infant respiratory distress syndrome and bronchopulmonary dysplasia (BPD), which occur most commonly in preterm infants and with effects spanning the pediatric-to-adult continuum. Gaps include lack of genetic and molecular markers of disease progression and suboptimal characterization of lung function over time. Potential solutions include the establishment of pediatric-to-adult transition and RRD clinics that minimize the loss to follow-up that occurs as patients exit pediatric care models and facilitate multidisciplinary translational research studies. For instance, the maximum potential FEV_1, as defined by the peak FEV_1 before decline begins (approximately age 24 yr), may differ among RRDs and could serve as an important surrogate endpoint for future decline or for assessing molecular and genetic markers of disease progression. In a cohort of 21-year-old patients with premature birth and BPD, the median maximum FEV_1 was 80% of predicted and was associated with greater airflow obstruction and bronchial hyperreactivity than in those subjects without BPD (21). The detailed characterization of transition cohorts would inform the development of surrogate markers of disease and the evaluation of novel therapeutic modalities.

Primary ciliary dyskinesia (PCD) is another RRD that begins in childhood and leads to chronic upper and lower respiratory infections caused by loss of ciliary function and defective mucociliary clearance (22). Little is known regarding the progression of lung function abnormalities into adulthood, and studies have thus far been limited by suboptimal pediatric-to-adult transition follow-up. The Genetic Disorders of Mucociliary Clearance Consortium and the PCD Foundation are currently focused on prospective evaluation of disease heterogeneity and genotype–phenotype correlation throughout the pediatric-to-adult spectrum (*see* section 4). Successes include establishing nasal nitric oxide as an effective screening test for PCD, evaluating inhaled hyperosmolar agents as a potential therapy, and identifying novel mutations in ciliary structure/function genes (*see* section 4) (23). The PCD Foundation has recently sponsored clinical guidelines for diagnosis and management (23), which promote awareness in the community and referral to tertiary clinical and translational research centers.

Clinical trials

As controlled experiments, randomized clinical trials can be leveraged to discover and evaluate novel disease mechanisms and biomarkers. The Multicenter International Lymphangioleiomyomatosis Efficacy of Sirolimus (MILES) trial investigators evaluated the efficacy of sirolimus for the prevention of lung function decline in patients with LAM (10). VEGF-D levels were elevated in patients with LAM but not in those with other cystic lung diseases (24), indicating its potential use as a diagnostic biomarker. In the MILES trial, the authors demonstrated a correlation between VEGF-D levels and decline in lung function or response to treatment (9). Researchers in future trials may use elevated VEGF-D levels as an enrollment criterion to both target the most appropriate patient population and optimize statistical power. Key points discussed are summarized in Figure 1.

Section 3: Preclinical Models and Mechanisms of Disease

The use of preclinical cell-based and animal models represents a crucial component in the translational research pipeline. Although they may not fully replicate human disease, preclinical models can be employed to (*1*) test mechanistic hypotheses generated from clinical observations; (*2*) discover new mechanisms of disease initiation, susceptibility, or progression; (*3*) conduct screens for novel therapies; and/or (*4*) identify or validate biomarkers and test the effectiveness of therapeutic approaches. In addition, these models can incorporate environmental factors (e.g., nutrition, stress) that interact with genetic determinants. Given the emphasis on molecular pathogenesis in RRDs, these models are well suited to complement RRD translational research platforms. Selected examples were discussed, and these are summarized below.

Cell-based assays and chemical screening

Translational investigators in CF, a protein-trafficking disease, have conducted cell-based drug screens using CFTR activity or subcellular localization as endpoints to identify potential "potentiator" or "corrector" drugs, respectively (14). Medium- to high-throughput ratiometric and electrophysiological cell-based assays (QPatch; Sophion Bioscience, Woburn, MA) were used to screen for CFTR correctors before validation of potential leads in standard epithelial ion transport assays. A primary airway cell biobank was established (Trans Canadian Network Initiative and McGill University Cystic Fibrosis Translational Research Centre) with seven distinct CF mutations represented, permitting the validation and testing of lead compounds and derivatives in patient-derived cultures. This platform was used for the preclinical development of latonduine, a proteostasis modulator and *bone fide* CFΔ508 corrector (25).

More broadly, systems biology and personalized medicine approaches provide a strong rationale for lead development and subsequent clinical trials. Genome-wide transcriptional profiling of CF cell lines with known CFTR mutations can complement chemical screens that both identify mutation-specific expression profiles and screen for drugs that may modulate these responses.

Stem cell and tissue engineering technologies can also be used to establish preclinical models and represent the developmental and genetic backgrounds of the aberrant disease-causing cell. Induced pluripotent stem cells can be engineered from patients before undergoing lineage-dependent differentiation to propagate cell cultures. In one study, induced pluripotent stem cell technology was used to re-create macrophages originally derived from a patient with hereditary pulmonary alveolar proteinosis (26). Reduced surfactant clearance in hereditary pulmonary alveolar proteinosis macrophages could be corrected by lentiviral expression of wild-type CSF2RA, thereby complementing the endogenous mutated form. This model can be used for drug screening, mechanistic studies, or transplant therapy (27).

Murine transgenic models for diseases of known genetic etiology

Murine models can be used to explore mechanisms of disease susceptibility arising from known human genetic mutations. Mutations in the *HPS1* gene cause

Hermansky-Pudlak syndrome, in which affected individuals develop severe pulmonary fibrosis. Although *Hps*-transgenic models do not spontaneously develop disease, they are more susceptible to injury-induced (e.g., bleomycin) fibrosis via a mechanism that requires epithelial cell apoptosis, as well as the subsequent profibrotic activation of alveolar macrophages (28–31). Genetic mutations seen in human subjects can be replicated in mouse models to explore mechanisms of disease and reveal additional cell-based or molecular therapeutic targets.

Murine models for RRDs with no unique molecular etiology

The absence of a defined disease-causing genetic mutation and the inability to fully reproduce pathological features of the human disease in mice present significant challenges. In idiopathic pulmonary fibrosis (IPF), the initiating event is not known, and murine models of fibrosis may use a variety of artificial induction agents to reproduce the pathophysiology. The routine use of inbred mice reduces experimental variability but does not address the genetic heterogeneity in human cohorts. Often, the timing or context of model initiation (e.g., age or sex of mice), interventions, or measurement of endpoints is not applicable to the clinical setting. Chronicity of the phenotype may hinder the use of fully representative experimental models because of animal care and use ethical guidelines, experimental complexity, or resource limitations. In IPF, researchers in translational studies have nonetheless attempted to focus on mechanisms of fibrosis and resulting loss of pulmonary function. These include aging-related susceptibility factors, aberrant epithelial cell function, and factors leading to excessive wound healing and lung remodeling (32). Murine models have been refined significantly by the use of repetitive induction (e.g., bleomycin [33]) and adenoviral gene transfer (e.g., adenoviral vector expressing human transforming growth factor-β [34]), as well as *in vivo* lineage tracing and stem cell technologies that permit the assessment of individual cell types over time (35). Contemporary murine studies incorporate chronicity, factors that initiate or promote fibrosis, interventional trial design, and clinically relevant endpoints that render the models translatable and amenable to the development of diagnostic biomarkers and therapeutics. As a result, translational animal experiments can complement successful large-scale human phase III studies (36, 37). Key points discussed are summarized in Table 1.

Section 4: Phenotyping and Biomarker Development

RRDs often exhibit significant phenotypic heterogeneity, which can be exploited to better understand mechanisms of disease or to design clinical studies that incorporate the analysis of outcomes in population subgroups. Modern high-throughput technologies permit large-scale DNA sequencing, which can link clinical phenotypes to a defined molecular etiology. Workshop participants discussed the paradigms described below to illustrate the utility of population phenotyping in RRDs and how this informs the development of well-defined surrogate endpoints for the effective design of clinical trials.

Phenotyping by respiratory function

The collection of granular physiological data over time (section 2) is crucial for understanding patient heterogeneity in RRDs. Patients with LAM exhibit different rates of decline in FEV_1 and diffusing capacity of the lung for carbon monoxide over time, which correlates directly with disease-related morbidity (38). These surrogate endpoints can be exploited to identify and characterize other biomarkers of disease severity, as well as to differentiate between responders and nonresponders to therapy. The surrogate endpoint approach can greatly reduce the sample size in clinical trials. Importantly, clinical trials in which changes in lung function in the placebo or treatment arms exhibit variability may yield negative results even if many of the patients respond to the intervention. In one study of patients with Hermansky-Pudlak syndrome, a salutary effect of pirfenidone on lung function did not achieve statistical significance; patient selection by prior rate of decline in lung function might have resulted in positive results, and pirfenidone could have been approved for this indication (39). Finally, novel clinical trial designs (e.g., N-of-1, crossover, adaptive) can complement the use of surrogate physiological endpoints in optimizing clinical and translational protocols (40, 41).

Using biomarkers to identify disease in presymptomatic patients

Another major challenge is to identify patients at risk for developing clinically significant disease so that prognostic and therapeutic tools can be employed early on. For instance, screening computed

Table 1. Preclinical models

Key Messages	Current Challenges
• Preclinical cell-based and animal models represent a critical component of the translational pipeline in RRDs.	• The development of appropriate animal models to study the effect of genetic variation and/or environmental factors on disease initiation or progression
• New technologies, improved study design, and the incorporation of chronicity permit the establishment of preclinical models that enhance the translational research effort even if they do not precisely replicate the human disease.	• The establishment of single-center or networked translational research platforms that incorporate patient care, cohort development, and preclinical investigations in the same pipeline to support multidirectional interactions in development of diagnostics and therapeutics
• Induced pluripotent stem cells and *in vivo* cell lineage tracking are promising technologies to characterize pathogenesis from early stages of disease.	• The formulation of standard protocols and endpoints for rapidly assessing the regulatory requirements for entry into human clinical trials

Definition of abbreviation: RRD = rare respiratory disease.

tomographic (CT) scans or serum VEGF-D levels in patients with tuberous sclerosis (i.e., at risk for LAM) might permit the identification and prognostication of patients who subsequently develop LAM. In a recent study with patients deemed at risk for familial pneumonitis syndromes on the basis of screening relatives of affected patients, investigators identified panels of clinical and molecular markers that predict the onset of CT scan abnormalities (42). These types of phenotyping studies can greatly facilitate the classification of patients in RRD research protocols.

Phenotyping by unbiased biomarker discovery

RRD networks and patient-based advocacy groups have contributed to the successful collection of biological samples with linked clinical data from natural history studies, registries, and clinical trials. Samples can be interrogated for genetic, transcriptomic, or molecular biomarkers in an unbiased fashion. In IPF, clinical outcomes were associated with molecular "endotypes" that reflect epithelial dysfunction and senescence, innate immune responses, and aberrant lung remodeling (43). Genetic, transcriptomic, and proteomic patterns can be used as quantitative surrogate endpoints for stratification in clinical trials and as clinical tools for prognostication (i.e., personalized medicine). This was illustrated in a study of *N*-acetylcysteine for IPF: A single-nucleotide polymorphism (rs3750920) in the *TOLLIP* gene predicted improved clinical outcomes in patients with IPF receiving *N*-acetylcysteine, whereas clinical outcomes were worse in those with the alternate allele (44, 45). In separate studies, transcriptomic patterns in peripheral blood mononuclear cells and telomere length have been associated with disease progression and/or acute exacerbations (46, 47). The enrichment of cohorts with potential responders to treatment might be achieved using biomarker panels that discriminate between IPF and other forms of interstitial pneumonitis (48) or those who are predicted to exhibit biological responses to therapy.

Phenotyping to discover rare variants of common diseases

The detailed phenotyping of common diseases can reveal rare variants that potentially shed important insights into disease pathogenesis. For instance, the interrogation of DNA from families with pulmonary fibrosis led to the identification of candidate genes for therapeutics and biomarker development (49). Detailed CT image analysis of patients within chronic obstructive pulmonary disease cohorts (i.e., the Multi-Ethnic Study of Atherosclerosis Lung Study) revealed that specific airway segmental branching variants were more common in patients with chronic obstructive pulmonary disease (B. M. Smith, oral communication, October 2015). These anatomical variants were in turn associated with single-nucleotide polymorphisms in a number of candidate genes, which encode protein mediators of lung development. Current studies addressing mechanisms of disease in respective mutant mice, as well as the natural history of obstructive airway disease in patients with these mutations, might provide important insights into factors that determine susceptibility to the initiation or progression of common airway diseases.

Genotype–phenotype correlation

Genotype–phenotype correlation is a promising approach to understanding mechanisms of disease and to classifying patients within cohorts that are genetically and phenotypically heterogeneous. A translational approach was formalized by the Genetic Disorders of Mucociliary Clearance Consortium and the PCD Foundation. Significant heterogeneity in the clinical features of PCD can arise from age of presentation, the presence and nature of anatomical lateralization defects, the severity of airway obstruction, upper airway infections, infertility, and gastrointestinal dysfunction (50, 51). Current diagnostic modalities are focused on ciliary structure and function, but they are often cumbersome and subjective; fail to capture the full spectrum of disease; and, especially in young children, do not effectively distinguish PCD from other syndromes with similar clinical presentations (e.g., CF). The complexity of ciliary composition amplifies the number of potential causative genes. Until 2008, identification of the first eight genes associated with PCD relied largely upon candidate gene-based approaches using model organisms and gene mapping by linkage analysis. Profiling of the two initially discovered genes (i.e., *DNAI1*, *DNAH5*) identified mutations in nine exons that were used in the first diagnostic test for PCD. Since 2009, the pace of discovery has been accelerated by next-generation sequencing technologies. Currently, 35 genes are known to be associated with PCD, accounting for approximately two-thirds of all PCD cases. Emerging insights into associations between genotype and phenotype are reviewed elsewhere (52). For example, there is a strong association between genotype and changes in ciliary structure and/or function, and nasal nitric oxide levels are usually low. *DNAH11* mutations, however, were observed in patients with normal ciliary ultrastructure (53). Patients harboring *RSPH1* mutations exhibited a milder pulmonary phenotype, and symptoms became prevalent with age (54). The identification of all disease-causing mutations in PCD is now feasible using current sequencing technologies, and correlations with phenotype will permit the optimization of counseling, prognostication, and design of future clinical and translational studies. Now commercially available, next-generation sequencing panels will also allow identification of cases that require whole-exome sequencing for novel gene discoveries. Key points discussed are summarized in Table 2.

Section 5: New Opportunities: Respiratory Manifestations of Rare Neuromusculoskeletal Diseases

Translational RRD research centers can leverage growing international patient cohorts, the power of patient advocacy, and expertise in preclinical and clinical research that addresses lung pathophysiology and respiratory clinical outcomes. Workshop organizers proposed that RRD translational research platforms can investigate rare neuromusculoskeletal diseases in which respiratory manifestations account for significant morbidity and mortality. As is the case for other multisystem disorders that significantly affect the lung (e.g., CF, tuberous sclerosis complex), RRD translational research programs could develop clinical cohorts and preclinical models, as discussed above, that inform the development of diagnostics and therapeutics for improving the

Table 2. Phenotyping and biomarker development

Key Messages	Current Challenges
• Simultaneous innovations in physiological, imaging-based, molecular, and genetic biomarker discovery have greatly improved patient care and facilitated the design of clinical trials using surrogate endpoints.	• Health disparities in the overall population related to age, race, sex, socioeconomic class, or geographical location complicate effective patient care and the recruitment of fully representative cohorts. Health disparities research might shed light on mechanisms to account for phenotypic and genetic variation in these populations.
• A common infrastructure for pediatric and adult RRDs could support bidirectional preclinical and clinical investigations, as well as mechanisms to screen for early markers of disease in otherwise asymptomatic patients.	• Despite the establishment of clinical networks, subcontracting and institutional review board agreements represent significant hurdles in conducting interinstitutional research. The formulation of widely adopted standard operating protocols, in addition to the use of centralized, multicenter processes, represents a promising approach.
• Detailed phenotypic analysis of common disease cohorts might reveal otherwise unknown rare diseases that provide translatable genetic and molecular insights.	

Definition of abbreviation: RRD = rare respiratory disease.

quality of life and survival of these patients.

Several examples of rare genetically inherited and metabolic myopathies that can present primarily with respiratory manifestations in adults were discussed (e.g., myotonic dystrophy, mitochondrial myopathy, McArdle disease) (55). Pompe disease, a glycogenosis caused by autosomal recessive mutations in the acid α-glucosidase (*GAA*) gene (56), was highlighted as a rare neuromuscular disorder that disproportionately affects the diaphragm. Studies indicate a correlation between GAA levels and the age of onset, as well as progression of respiratory muscle dysfunction. Exercise limitation, sleep-disordered breathing, and aspiration pneumonia are also associated with increased morbidity and mortality. Recombinant human GAA therapy slows the loss of pulmonary function (57), but diagnosis and treatment are often delayed. In addition, detailed, long-term, respiration-focused physiological and biological markers of disease progression and response to established or novel therapies are lacking. These can potentially be developed in the context of multinational collaborations, special needs RRD clinics, and translational research platforms.

Rare disorders of bone formation and aberrant matrix production can also result in chronic respiratory failure and sleep-disordered breathing on the basis of chest wall and/or parenchymal restriction. Osteogenesis imperfecta (OI) is a genetically inherited disease of bone fragility that is usually caused by mutations in the collagen type I genes (*COL1A1*, *COL1A2*), with typical skeletal and extraskeletal manifestations (58). Translational research efforts in OI have been championed by the Osteogenesis Imperfecta Foundation and the Shriners Hospitals for Children Network. Consistent genotype–phenotype correlation and sensitivity of genetic testing have defined a rich cohort in which to study natural history and potential therapies. Little is known regarding changes in lung physiology and gas exchange over time in patients with OI, but respiratory dysfunction appears to be a frequent cause of death (59, 60). A crude analysis of 92 adults suggested a correlation between scoliosis and reduced lung function when corrected for arm span (61). Based on spirometry, there was evidence of obstructive airway abnormalities in a significant proportion of patients, even in the absence of scoliosis, suggesting direct involvement of the lung. The detailed characterization of pulmonary function and gas exchange over time in existing preclinical OI models and genetically well-defined clinical cohorts may provide important insights into the evolution of pulmonary disease in patients with OI or other diseases of chest wall restriction.

Summary

Translational research in RRDs has led to an explosion in novel diagnostic and therapeutic approaches for previously neglected patients. Optimal RRD translational research programs require a coordinated and multidisciplinary approach that relies on an integrated infrastructure. Effective translational research programs in RRDs are managed by dedicated clinicians/scientists and coordinators who facilitate communications and collaboration with transnational research networks, patient advocacy groups, and policy makers. Preclinical models of RRDs and patient cohort phenotyping are critical in determining the link between molecular pathophysiology and disease classification, respectively. The development of screening assays and surrogate physiological or biological markers facilitates drug development and the design of clinical trials, as well as screening/diagnosis and disease monitoring. Current gaps include the detailed characterization of subjects transitioning from pediatric to adult care; the coordination of special needs multidisciplinary clinics; regulatory hurdles impeding interinstitutional collaboration and drug or diagnostics development; and novel clinical trial designs that overcome chronicity, heterogeneity, and effects of cointerventions. Finally, it was proposed that translational research platforms in RRDs, which include multisystem disorders that impact significantly upon the lung, could incorporate subjects with rare neuromusculoskeletal diseases and potentially lead to the conduct of research that ultimately has a positive impact on their quality of life and survival. ■

This official Workshop Report was prepared by an *ad hoc* committee of the Assembly on Respiratory Cell and Molecular Biology.

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