A Perspective: Division of Lung Diseases at Fifty

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In 1969, the U.S. space program put a man on the moon; 400,000 people gathered in the pouring rain in Bethel, New York, to listen to music; and the “Miracle” New York Mets unexpectedly won the World Series. Also in 1969, the Secretary of Health, Education, and Welfare expanded the 21-year-old National Heart Institute to become the National Heart and Lung Institute (NHLI) to consolidate pulmonary research from across NIH under one office. Over the last 50 years, this office, which became the Division of Lung Diseases (DLD) in July 1972, has grown from a budget of \$5 million to one of \$734 million in 2018, has released over 350 initiatives, and has expanded to now fund about 1,800 grants and contracts each year. Simultaneously, attendance at the annual American Thoracic Society meetings has soared from approximately 2,000 in 1969 to over 16,000 in 2017. Many partners and stakeholders have contributed to this growth and progress. This perspective highlights DLD’s role among them in implementing a collective and coordinated vision for NIH extramural pulmonary research.

From the very beginning, DLD engaged stakeholders for advice on research programs through a series of task forces. The first, convened in 1969, brought together government agencies and professional societies; the second brought together U.S. pulmonary program directors; and a third, chaired by Dr. Claude Lenfant, who had arrived in 1970 as Associate Director for the Lung Programs, focused on respiratory medicine (1). By the time President Richard

Nixon signed the National Heart, Blood Vessels, Lung, and Blood Act in September 1972, DLD had received input from hundreds of stakeholders that established foundational guiding principles for the DLD (2).

These early recommendations emphasized the importance of 1) elucidation of basic processes as a key to developing treatments, 2) research that can inform patient care and well-being, 3) partnerships and multidisciplinary teams, 4) training in the latest techniques and their application at the community level, and 5) development of new methods to inform the research of tomorrow. The five research areas outlined in this perspective illustrate the DLD’s continued adherence to these principles and its use of focused programs and initiatives to advance pulmonary science and medicine.

Infant Respiratory Distress Syndrome: From Physiology to Molecules

In the 1960s, whole organ and organism physiology dominated respiratory research. This had begun to change with Dr. John Clements’s findings that the low surface tension of lung extracts could explain why lung elasticity did not lead to alveolar collapse (3). Following on Dr. Clements’s work, Dr. Mary Ellen Avery showed that the surface tension of premature infants dying of hyaline membrane disease was high compared with that of adults, children,

or infants dying of other causes (4), suggesting an absence of this low surface tension material called “surfactant.” The exciting therapeutic potential of findings such as these led the task force panel members to comment, “Pulmonary physiology has contributed greatly to an understanding of clinical problems.... But with the emergence of new developments at the cellular, ultrastructural and molecular level, channels have opened for innovative approaches of great promise” (5).

To encourage new approaches for discovery and translation, the NHLI released its first solicitation for Specialized Centers of Research (SCOR) in pulmonary diseases in 1970, requiring at least one clinical project related to the basic research. Under iterations of this program, investigators established the role and safety of glucocorticoids in the maturation of the human lung (6, 7), leading the NHLI to release a request for proposals in 1975 to study the efficacy of antenatal steroids in the prevention of neonatal respiratory distress syndrome. This program confirmed the role of steroids in accelerating lung maturation.

Other work improved techniques for prenatal assessment of lung maturation using amniocentesis (8), characterization of surfactant and its associated proteins (9), and new methods for the isolation of type II cells for *in vitro* studies of lamellar bodies as the source of surfactant (10). Continued basic and clinical research collaboration in the SCOR programs led to the synthesis and early testing of a protein-free synthetic

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A complete list of 2018 members of the NHLBI Division of Lung Diseases staff may be found before the beginning of the REFERENCES.

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surfactant suitable for large-scale production (11). The commercial availability of synthetic surfactants, coupled with new management techniques, has led to dramatic reduction in the mortality of premature infants. More recent NHLBI programs have focused on preventing bronchopulmonary dysplasia (BPD), defining BPD phenotypes, and improving understanding of lung development, as well as ventilatory control in prematurity.

Acute Respiratory Distress Syndrome: The Importance of Understanding Basic Processes to Develop Effective Treatments

One of the very early NHLI initiatives, released in December 1972, was a request for proposals for a clinical trial using extracorporeal membrane oxygenation to bypass the lungs during severe respiratory failure. When early results showed >90% mortality and no benefit of extracorporeal membrane oxygenation (12), DLD and the research community decided that understanding the underlying acute respiratory distress syndrome (ARDS) pathophysiology could elucidate possible treatments. DLD convened a group of 30 investigators to develop recommendations regarding future research in ARDS. The publication of the conference summary and recommendations became DLD's standard practice for its conferences and workshops (13).

Pursuant to these recommendations, DLD released several requests for applications (RFAs) targeting pathogenesis and mechanisms underlying acute respiratory failure, leading to new research in barotrauma, volutrauma, vascular permeability, and ARDS prevention. Early work demonstrated that ventilation of normal rat lungs with high airway pressure (45 cm H₂O) without positive end-expiratory pressure (PEEP) induced severe acute lung injury and death, whereas ventilation with lower airway pressure did not (14); the addition of PEEP to high airway pressure conferred protection. Subsequent work determined that large lung volumes induced injurious volutrauma (15). The importance of vascular permeability as a modifiable factor became especially apparent with research examining Starling forces in which lower

vascular pressure reduced transvascular fluid filtration and subsequent pulmonary edema, particularly in the presence of increased lung vascular permeability (16). Furthermore, animal studies demonstrated that reduced lung vascular pressure can attenuate lung endothelial translocation of P-selectin and resultant accumulation of intravascular neutrophils (17), thus mitigating the severity of neutrophil alveolitis.

These findings suggested new management approaches, but clinical trials in lung diseases were still uncommon, and even less common in the critically ill. In 1994, DLD launched the ARDS Network (ARDSNet), the first multicenter network designed specifically to support clinical trials in patients with ARDS. ARDSNet conducted many important studies, including two that changed the standard of care in ARDS. The trial of ventilation with lower V_Ts than with traditional V_Ts used for acute lung injury and ARDS (ARMA [2000 ARDSNet trial]) demonstrated a 9% reduction in mortality with lower V_Ts than with traditional higher V_Ts (18), and a trial comparing two fluid management strategies in acute lung injury (FACTT [Fluids and Catheters Treatment Trial]) demonstrated that a conservative fluid strategy increased the number of ventilator-free days compared with a liberal fluid strategy (19).

Asthma: From Understanding Basic Processes to Public Health

Asthma research provides illustration of the DLD's role in facilitating basic discovery; its translation to patient care; and, ultimately, implementation to public health. The very first RFA published by DLD (also the first from NIH) was broad, requesting studies of inflammation in the lung ([see grants.nih.gov/grants/guide/historical/1975_10_22_Vol_04_No_09.pdf](https://grants.nih.gov/grants/guide/historical/1975_10_22_Vol_04_No_09.pdf)). None of the grants awarded were intended for the study of asthma, because asthma research was not focused on inflammation. Nevertheless, studies using ovalbumin-sensitized rabbits to examine the pulmonary vasculature revealed that ovalbumin treatment of the *ex vivo* lungs produced significant increases in airway resistance (20). Other investigators reported that ozone exposures, designed to induce lung inflammation, caused an increase in

airway resistance (21). New studies showing an association between serum IgE levels and the presence of asthma indicated a role for allergic pathways that were known to be steroid sensitive (22). Collectively, these studies pointed to a role of inflammation in asthma and a potential benefit of inhaled corticosteroids.

Despite the approval of inhaled corticosteroids for asthma in 1980, national statistics showed increasing prevalence, healthcare use, costs, and mortality associated with asthma (23), prompting the establishment of the National Asthma Education Program (NAEP) (24). NAEP, modeled on successful education programs in cholesterol and hypertension, brought together 20 professional and lay organizations to raise awareness and coordinate education of health professionals, patients, and the public about asthma and its control. One of the NAEP's first activities was to issue an expert panel report on the diagnosis and management of asthma (25). NAEP, now called the "National Asthma Education and Prevention Program," has expanded to over 40 partners, has updated treatment guidelines three times, and is currently working on a fourth update on selected topics (26).

As in ARDS, DLD was supporting few clinical trials in the management of asthma through the early 1990s, so DLD launched the Childhood Asthma Management Program, followed quickly by two clinical research networks to study the clinical management of asthma, one in adults and one in children. The Childhood Asthma Management Program established that inhaled budesonide was well tolerated and decreased the need for rescue therapy with systemic prednisolone (27). This trial and those conducted through the DLD-supported networks have made major contributions to clinical practice guidelines that are widely accepted as standard of care for asthma (28).

Cystic Fibrosis: Partnering with Multiple Stakeholders and Hand Offs

The ARDS and asthma histories illustrate how DLD partners with the research community, other government agencies, professional societies, and public interest organizations. Cystic fibrosis (CF) research

illustrates DLD's role in multiple interlocking partnerships and hand offs that yielded new treatments and led to increases in the life expectancy of patients with CF. DLD's contribution to CF began soon after the founding of the division with release of several RFAs focused on cellular models of the disease and creation of several SCOR centers on CF as well as program project grants and investigator-initiated R01 grants.

Research developed from these targeted initiatives enabled investigators at the University of Iowa to study CFTR (cystic fibrosis transmembrane conductance regulator) function after expressing CFTR in cultured cells. These investigators demonstrated that CFTR activity could be modulated, in this case by trypsin (29), raising the possibility of pharmacologic modulation. Investigators at the University of North Carolina studied the electrophysiology of CFTR and showed that the net effect of CFTR expression was depolarization of the cell membrane (30). Investigators at Johns Hopkins University showed that different CFTR mutants behaved differently; in this case, the G551D mutant could be inserted in the cell membrane but had lower net conductance than the wild-type channel (31). These three lines of evidence all converged in the development of ivacaftor. Scientists at the company Vertex developed a cellular model by expressing the G551D mutant in cells and using a membrane potential-sensitive dye to monitor activity of the CFTR ion channel (32). Using this model system, they screened tens of thousands of small molecules in work that led eventually to the discovery of ivacaftor, to clinical trials, and to very rapid U.S. Food and Drug Administration approval of this novel drug (33). Although ivacaftor was developed by industry, most of the underlying science came from academic researchers, and much of the support for that research came from DLD, other institutes of the NIH, and the Cystic Fibrosis Foundation. This pyramid of support illustrates the importance of cooperation and partnering in biomedical research.

Sleep and Circadian Rhythm: Informing the Research of Tomorrow

In 1993, Congress called for the establishment of the National Center on Sleep Disorders

Research within NHLBI because of rising concerns over sleep health. The National Center on Sleep Disorders Research initially focused on public awareness and education about sleep and identifying the health effects of poor sleep. The NHLBI launched the multisite Sleep Heart Health Study (SHHS), leveraging existing NHLBI cohorts to quantify prospectively the mortality and comorbidities associated with sleep apnea in a community cohort of middle-aged adults (34). SHHS discovered that all-cause mortality was higher in subjects with clinically significant apnea and that the risk of death increased with apnea severity (35). In the Year 16 follow-up, subjects with severe apnea were nearly 46% more likely to have died than those with no apnea at baseline (35). The Wisconsin Sleep Cohort Study uncovered for the first time the high incidence of sleep apnea in middle-aged adults and the strong association of apnea with gender and obesity (36). Imaging studies revealed profound structural differences of the upper airways between adults with and without obstructive sleep apnea (37). A recently published analysis of the SHHS data suggests that positive airway pressure therapy for sleep apnea reduces all-cause mortality, extending life by 6–7 years (38).

The understanding of sleep and its importance to health was facilitated by the discovery of the CLOCK (clock circadian regulator) gene and the network of transcription factors governing the order of gene expression in the brain and nearly all tissues (39). Michael Rosbash, Jeffrey Hall, and Michael Young elucidated molecular mechanisms controlling circadian rhythm, earning them the 2017 Nobel Prize in Physiology and Medicine. They reasoned that PER (Period) protein could prevent its own synthesis and thereby regulate its own level in a continuous, cyclic rhythm, which is now known to be the core of the circadian clock (40). These and other seminal discoveries have led to the realization that sleep and circadian biology are crucial to many fundamental cellular and physiological functions.

Across Diseases

We have selected just five research areas from among many possible examples to illustrate DLD's contribution to the evolution and progress in lung research and public health (Figure 1). With guidance

from the initial task forces, DLD programs in the first epoch steered the research community from whole-organ physiology to cellular work, always with an eye to translation to patients. SCOR programs spanning the decades 1970–2009 contributed to progress in BPD, pulmonary hypertension, interstitial fibrosis, acute lung injury, asthma, CF, and chronic obstructive pulmonary disease (COPD), to name just a few. The SCOR program and subsequent Specialized Centers of Clinically Oriented Research programs can be viewed as parents of our current Centers for Advanced Diagnostics and Experimental Therapeutics. Recognizing that basic research had become self-sustaining and that there were still few clinical trials in the management of pulmonary diseases, DLD released initiatives, starting in the 1990s, to encourage clinical trials. As investigator-initiated multicenter clinical studies have thrived, we have sunset some of these clinical networks. The wide variability in outcomes and phenotypes among patients observed in these clinical trials led DLD to release initiatives in the early 2000s aimed at defining and understanding heterogeneity within diseases and identifying targets for novel and personalized management, such as SPIROMICS (Subpopulations and Intermediate Outcome Measures in COPD Study) and PVDomics (Redefining Pulmonary Hypertension through Vascular Disease Phenomics).

In parallel to these initiatives were programs aimed at training for the research of tomorrow. Early training programs, like the scientific programs, were aimed at building a dedicated pulmonary research community. The first training program, the Pulmonary Academic Award in 1970, sought simply to foster academic careers in the respiratory field. As specific research needs and gaps were identified, training programs focused on specific areas within pulmonary research. Today, the pulmonary research community is strong, self-sustaining, and able to leverage general training programs across NHLBI and NIH. Now, DLD supports over 500 active training awards across 17 different training mechanisms.

Future Directions

The principles established in those initial task forces are still relevant looking forward.

Figure 1. Graphical history of NHLBI's Division of Lung Diseases (DLD). (A) Time trend of DLD funding of extramural research for the period 1969–2018. (B) Selected representative initiatives developed and funded by DLD that reflect the evolving nature of pulmonary research over the past five decades. Initially, DLD focused on establishing a robust research community at the cutting edge of science by steering investigators from physiology to more basic and cellular work and encouraging research training (not shown). Early initiatives focused on identifying lung cells and basic mechanisms, gradually over time focusing on particular diseases and conditions. In the second era, starting in the early 1990s, DLD addressed the paucity of investigator-initiated clinical trials in lung disease by releasing initiatives for clinical research networks. These clinical trial results revealed the heterogeneity of responses to treatment and led to the third and current era with the development of programs defining phenotype–genotype relationships as a first step toward identifying targets for novel and personalized treatments. Full names of the programs identified by acronyms in the figure are given in the appendix in the online supplement.

NHLBI underwent a yearlong strategic visioning exercise in 2016 (41). Like the NHLBI report in 1973, the developers of this strategic vision solicited input from many stakeholders. Using modern crowdsourcing methods, we received comments from over 4,000 stakeholders in all 50 states and 42 countries around the world. From this report, DLD has derived four main strategic priorities: prevention, precision medicine, implementation, and regeneration. As in the past, DLD priorities remain focused on basic discoveries, their translation, and clinical studies to improve patient care and public health. Principles articulated at the birth of DLD remain: developing multidisciplinary teams, training the next generation of researchers, advancing knowledge of cellular and molecular networks or systems, capitalizing on the emerging approaches (e.g., “trans-omics” and data science), continuing the strong community engagement, and performing ongoing evaluation of DLD programs.

Ultimately, the vision of DLD is to prevent lung disease development. The most effective preventive measure remains smoking cessation even after established disease (42). DLD has released initiatives to identify other modifiable factors (RFA-HL-15-024 and RFA-HL-15-025). Many studies have suggested that good lung health in adulthood actually starts at or before birth (43). Adults who had BPD as neonates are at higher risk for adult-onset COPD (44). With survival of babies now as young as 23–24 weeks of gestational age, new issues in the underdeveloped lung are being uncovered. Just as understanding surfactant biology led to new treatments and prevention in the 1980s and 1990s, we expect understanding of lung development will lead to new treatments and prevention in the future. The Molecular Atlas of Lung Development Program (LungMAP), now in its second phase, is building a comprehensive, publicly accessible molecular atlas of early- and late-stage human lung development that will serve as a critical reference platform for understanding both normal human lung biology and disease pathogenesis (3).

For precision medicine, the interest in the heterogeneity of individual responses goes back at least to 1991, when DLD released an RFA on the genetics of asthma (RFA-HL-92-04-L). Patients with a gene expression profile consistent with T-helper

cell type 2 inflammation are more likely to respond to inhaled fluticasone (45). In parallel work, DLD's Severe Asthma Research Program has extensively phenotyped hundreds of individuals with severe asthma and shown that their characteristics cluster into about five groups, likely differing in pathobiology (46). Building on the Severe Asthma Research Program's findings, DLD recently created a new network, called "Precision Interventions for Severe and/or Exacerbation Prone Asthma" (PrecISE), which will be conducting an adaptive, biomarker-directed clinical trial to test a more personalized approach to asthma management (preciseasthma.org/preciseweb/). Similar research is being done for other diseases, including DLD-initiated multicenter programs for deep phenotyping in COPD and pulmonary hypertension and investigator-initiated programs for phenotyping BPD, CF, idiopathic pulmonary fibrosis, and sleep disorders. This research will lay the groundwork for the development and testing of precision treatments based on cellular and molecular phenotypes.

DLD is pursuing implementation research to help increase adoption of and adherence to evidence-based practice by better understanding the barriers and facilitators. DLD has initiated the Asthma Empowerment Program (RFA-HL-17-001), a program in asthma that evaluates the process and effect on clinical outcomes of integration of interventions from at least four different sectors that contribute to the care of children with asthma: medical care, families, home environment, and the community. A similar program has been initiated for inpatient diseases, including ARDS (RFA-HL-18-018), in which adherence to evidence-based therapy such as low-V_T ventilation is low (47, 48).

The roots of DLD's interest in lung regeneration dates to DLD's inception, when interest related primarily to identifying and characterizing cells of the lung (RFP-NHLI-73-21). By the early 2000s, NHLBI had released a funding opportunity announcement (RFA-HL-02-004) for exploratory grants to develop new approaches to engineering tissue *in vitro* as a biological substitute for implantation or to fostering tissue regeneration *in vivo*. In 2012, to help the lung research community with its specific, unique barriers, DLD released its own program, the Lung Repair and Regeneration Consortium (RFA-HL-12-006 and RFA-HL-12-010). Progress made in that program facilitated DLD's joining the 2016 NHLBI Progenitor Cell Translational Consortium to leverage the advances in basic progenitor biology for new regenerative therapeutic strategies for heart, lung, and blood disorders. DLD has continued to lead in lung regeneration biology by supporting additional lung-specific programs, including the Impact of Microenvironment on Lung Progenitor Cell Function (RFA-HL-18-022).

Our goals for the next half-century will be to foster cutting-edge research while maintaining close attention to the everyday needs of patients. For example, research on how sleep deficiency influences gene transcription and how the abnormalities that sleep deficiency produces in clock-ordered gene expression are associated with disease, pathobiology, and the efficacy of therapeutic interventions presents new avenues for the development of biomarkers and improvement in the treatment of sleep disorders as well as lung and other diseases (49). Elucidation of mechanistic sleep and circadian connections that affect disease opens new avenues to advance both personalized medicine and population health surveillance. Similarly, as research

uncovers new COPD phenotypes, DLD is working to apply that knowledge through the COPD National Action Plan, bringing together stakeholders across the government, public interest groups, professional societies, and patients and their families to identify priorities of people with COPD.

In closing, DLD's success over the past 50 years has been possible only through the creativity, vision, and perseverance of many staff working in concert with the scientific community. Behind each initiative and each program and for every grant or contract are DLD staff scientists committed to NHLBI's mission, working with you and for you as well as for the broad stakeholder community to find cures for respiratory diseases and associated disorders. We look forward to partnering with all as we work to improve respiratory health for the next 50 years and beyond. ■

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