Update From the NHLBI on Lung Vascular and Pulmonary Hypertension Research

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Over the past decade, significant advances in treating pulmonary arterial hypertension (PAH) patients have occurred. These advances have come as a result of collective efforts by physicians, scientists, patient advocacy organizations, pharmaceutical companies, and public and private grants-awarding agencies. The National Institutes of Health (NIH) registry was instrumental in characterizing the devastating nature of this disease[1] and National Heart, Lung, and Blood Institute (NHLBI)-supported research on the cellular and molecular mechanisms underlying basic pulmonary vascular tone regulation and abnormal vasoconstriction have been pivotal in identifying the therapeutic potential of the PAH drugs now in clinical practice. With the new therapies, the prognosis of PAH is improving and predictors of poor clinical prognosis have become better appreciated. However, better disease phenotyping, elucidating pathogenesis, and decreasing morbidity and mortality remain as research goals. The limitations of current therapeutic options necessitate that lung vascular and pulmonary hypertension research remains a high priority for the NHLBI.

NATIONAL INSTITUTES OF HEALTH MISSION AND CONTEMPORARY ACTIVITIES IN PULMONARY HYPERTENSION

The National Institutes of Health (NIH), a part of the US Department of Health and Human Services, is the nation's medical research agency. The NIH is the largest source of funding for medical research in the world, funding thousands of scientists in universities and research institutions. The NIH's mission is to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce the burdens of illness and disability. The NIH is composed of 27 institutes and centers, each with a specific research agenda, often focusing on particular diseases or body systems. The National Heart, Lung, and Blood Institute (NHLBI) is one of the component institutes; its mission is to provide global leadership for research, training, and education programs which promote the prevention and treatment of heart, lung, and blood diseases. The Division of Lung Diseases (DLD) within the NHLBI is responsible for administration of the extramural portfolio in lung diseases research, which includes diseases of the airways, interstitial compartments and cells, and the lung vascular systems. Additional information about the NIH and its mission, its collective institutes and centers, and the DLD can be found online by accessing the following Web page and its associated links: http://www.nih.gov/index.html.

The NIH recently identified 5 areas of promise for advancing biomedical research in the near future.[2] The NHLBI strategic plan is aligned to these 5 areas, which include: 1) capitalizing on high-throughput technologies, 2) fostering translational medicine, 3) performing research beneficiary to the cause of US health care reform, 4) performing research focused on global health, and 5) improving the research base by reinvigorating and empowering the biomedical research community. NHLBI-sponsored research programs and initiatives are designed to foster ongoing efforts in these areas of promise specific to heart, lung, and blood diseases. Programs and initiatives originating from within the DLD likewise align to the strategic plan and goals of the NHLBI and NIH. Furthermore, the DLD strategic plan for advancing lung disease research involves a multidisciplinary approach to program development, so as to generate robust support mechanisms for the lung investigative community (Figure 1).

The NHLBI currently supports an expanding program in pulmonary hypertension (PH) research. The NHLBI funded approximately $33.3 million in fiscal year (FY) 2008 and $41.4 million in FY 2009 in PH research projects. With therapies newly available for treating Category 1 PH (pulmonary arterial hypertension, or PAH),[3] the prognosis of PAH is improving, with an approximately 85% survival rate at 1 year.[4] However, the problems of diagnosing, treating, and ultimately curing PAH remain. As such, the NHLBI supports basic science in lung vascular biology and disease with projects that: 1) discover and define lung vascular biology and factors contributing to development of lung vascular disease; 2) focus on cellular, molecular, and genetic factors contributing to PAH pathogenesis including high-throughput technology-based projects; and 3) advance the paradigm of PAH as a vasculoproliferative disease, allowing for novel therapeutic target discovery. In addition, translational projects are: 1) advancing diagnostics and disease monitoring, 2) testing novel hypotheses of disease etiology, and 3) proposing novel end-point measures for use in subsequent clinical trials. While the breadth of the entire portfolio cannot be presented in this article, the aforementioned general examples are representative of multiple ongoing projects.

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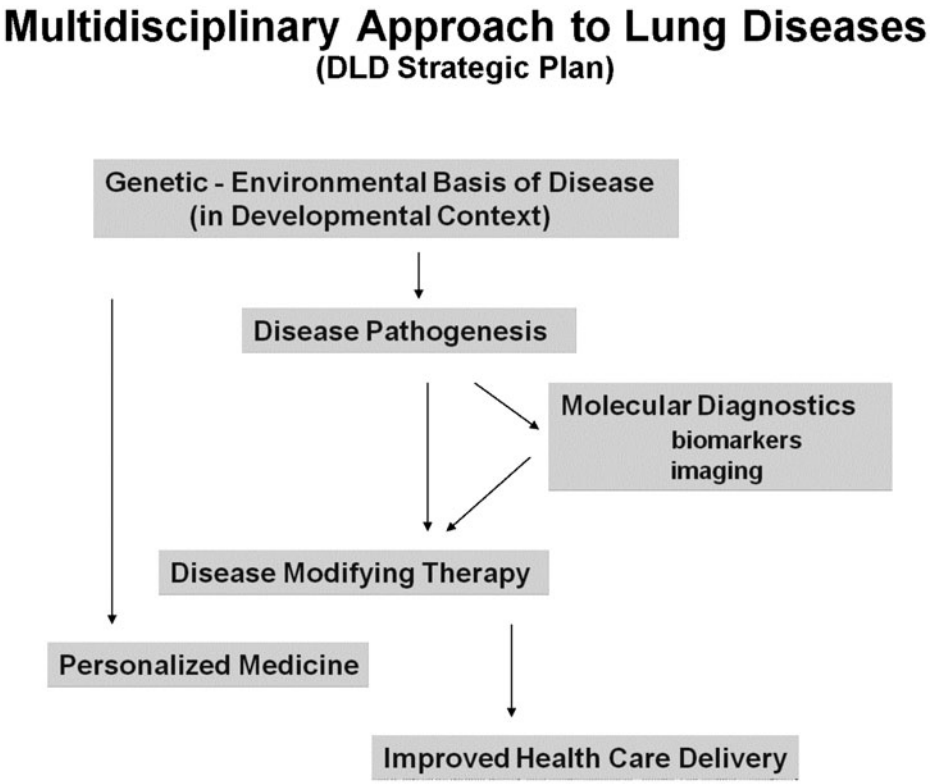

Figure 1: In alignment with the mission of the NHLBI and NIH, program development activities involve DLD staff working with the pulmonary community to identify the most important or pressing priorities and opportunities for future research. Current strategies support multidisciplinary approaches that provide exchange of expertise and ideas from different areas of the research community. Fostering the research that defines the genetic-environmental basis of disease, ie, basic discovery including lung developmental biology, is critical. Programs and initiatives may target knowledge gaps or encourage tools development at many points along the route from "Disease Pathogenesis" to "Improved Health Care Delivery." This paradigm results in strategic support ideas for molecular diagnostics, disease-modifying therapies, and personalized medicine. Plans will be adapted for or catered to specific lung diseases such as asthma, COPD, interstitial fibrosis, and/or pulmonary hypertension.

THE AMERICAN RECOVERY AND REINVESTMENT ACT OF 2009

The American Recovery and Reinvestment Act of 2009 (ARRA) provided a special opportunity to foster and promote new research across the NIH. The scientific community of investigators working on PH competed very successfully for support via ARRA funding mechanisms, and support for PH research amounted to approximately $5.9 million in new grants. Examples of ARRA-supported research include projects that: 1) use nanotechnology to assign vascular-specific "zip codes" to deliver disease-modifying therapies when they become available, 2) use stem cells "loaded" with currently available PAH drugs to hone directly to diseased vessels for providing direct and sustained treatment, and 3) identify novel disease biomarkers to help guide physician decision-making for treating children with PAH. A summary of the ARRA investment in NIH research including PH can be found online at: http://report.nih.gov/recovery/investmentreports/.

FUTURE DIRECTED ACTIVITIES IN LUNG VASCULAR RESEARCH

The NHLBI, with support from the Office of Rare Diseases Research (ORDR), held a workshop in March 2010 to identify priority areas for future lung vascular research. A report was generated for the investigator community for the purposes of enhancing and accelerating research that will result in improved understanding of the lung vasculature, translation of basic science findings, and the care of patients with pulmonary vascular diseases.[5] Multidisciplinary experts with diverse experience in laboratory, translational, and clinical studies identified the priority areas and further discussed limitations in our current knowledge, technologies, and approaches to lung vascular research. The focus for future research efforts were summarized to include: 1) better characterizing vascular genotype-phenotype relationships and incorporating systems biology approaches when appropriate; 2) advancing our understanding of pulmonary vascular metabolic regulatory signaling in health and disease; 3) expanding our knowledge of the biologic relationships between the lung circulation and circulating elements, systemic vascular function, and right heart function and disease; 4) improving translational research for identifying disease-modifying therapies for the pulmonary hypertensive diseases; 5) establishing an appropriate and effective platform for advancing translational findings into clinical studies testing; and 6) developing the specific technologies and tools that will be enabling for these goals, such as question-guided imaging techniques and lung vascular investigator training programs.

For each of the proposed lung vascular research priorities, an emphasis on PAH emerged. Several translational research opportunities were identified for PAH, as was the emerging opportunity to ask novel clinical research questions while seeking disease-modifying therapies. In response to the recommendations from the workshop panel, a strategic plan is being formulated to be consistent with the overall mission of the DLD, NHLBI, and NIH. The emerging plan includes actions for supporting basic, translational, and clinical research in PH. A summary of the workshop recommendations and matching support activities ongoing or in preparation can be found in Table 1.

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Table 1: A summary of the major recommendations from "Strategic Plan for Lung Vascular Research: An NHLBI-ORDR Workshop Report." RFAs (requests for applications) and PAs (program announcements) that address the recommendations are provided

Workshop Recommendation	Action Taken
-Advance basic scientific research in lung vascular biology utilizing emerging technologies -Develop strategies using appropriate animal models to improve the understanding of the lung vasculature in health and in conditions that reflect human disease	-Support meritorious investigator-initiated science (Parent R01, R21, P01, etc)
-Encourage systems analysis to understand and define interactions between lung vascular genetics, epigenetics, metabolic pathways, and molecular signaling	-PAR-09-214 – NHLBI Systems Biology Collaborations (R01)
-Enhance translational research in lung vascular disease by comparing cellular and tissue abnormalities identified in animal models to those in human specimens	-PAR-09-185 – Translational Programs in Lung Diseases (P01) -RFA-HL-11-015 – Centers for Advanced Diagnostics and Experimental Therapeutics in Lung Diseases Stage I (P50) -RFA-HL-11-032 – Utilization of a Human Lung Tissue Resource for Vascular Research (R03)
-Advance and coordinate basic and clinical knowledge of the pulmonary circulation-right heart axis through novel research efforts utilizing multidisciplinary teams	- Develop a pulmonary vascular–right ventricular axis research program
-Develop in vivo imaging techniques that assess structural changes in lung vasculature, metabolic shifts, functional cell responses, and right ventricular function	-Develop a lung molecular imaging program
-Define interactions between lung vascular components and circulating elements and systemic circulations by fostering novel collaborations	-RFA-HL-12-006 – Consortium of Lung Repair and Regeneration: Building the Foundation (U01)
-Develop research consortia that advance basic, translational, and clinical studies, allow for multicenter epidemiological study feasibility, and support junior investigators' training in lung vascular biology and disease, and improve lung vascular disease molecular and clinical phenotype coupling	-PAR-10-005 – NHLBI Clinical Trial Pilot Studies (R34) -RFA-HL-11-006 – Next Generation Association Studies (U01) -Develop a pulmonary hypertension research consortium

References

1. D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med.* 1991;115(5):343-349.

2. Collins FS. Research agenda. Opportunities for research and NIH. *Science.* 2010;327(5961):36-37.

3. Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol.* 2009;54(1 Suppl):S43–S54.

4. Humbert M, Sitbon O, Chaouat A, et al. Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. *Circulation.* 2010;122(2):156-163.

5. Erzurum S, Rounds SI, Stevens T, et al. Strategic Plan for Lung Vascular Research: An NHLBI-ORDR Workshop Report. *Am J Resp Crit Care Med.* 2010 Oct 8. [Epub ahead of print]

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