Specialized Centers of Clinically Oriented Research Programs in Pulmonary Hypertension Reported Progress at the PHA Scientific Sessions

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Recently, the National Heart, Lung, and Blood Institute awarded 2 Specialized Centers of Clinically Oriented Research (SCCOR) program grants in pulmonary hypertension. The SCCOR program requires clinical and basic scientists with a broad range of skills to work together on a unified theme, with special emphasis on clinically relevant research.

The goal of the SCCOR program is to encourage multidisciplinary research on clinically relevant problems to allow basic science findings to be more rapidly applied to clinical situations. It is expected that over 50% of the funded research is clinical and interactions between clinical and basic scientists are expected to strengthen the research, enhance the translation of fundamental research findings to the clinical setting, and identify new research directions. In addition, each SCCOR project must have a defined organizational and administrative structure to enhance and enable interactions between investigators to increase the rate of translation of basic research findings to clinical applications.

At the recent Scientific Sessions at the Pulmonary Hypertension Association 8th International Conference, the principal investigators for the 2 SCCOR programs in pulmonary hypertension—Dr Paul Hassoun from Johns Hopkins University and Dr Kurt Stenmark from the University of Colorado Denver School of Medicine, reported on progress made in each of their research programs. These are summarized in the following reports.

National Heart Lung and Blood Institute Hopkins Specialized Center in Clinical Oriented Research (SCCOR): Molecular Determinants of Pulmonary Arterial Hypertension

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SCCOR Investigators: Paul M. Hassoun: overall Principal Investigator, Project 1 leader and administrative core leader; Hunter C. Champion: Project 2 leader; Fredrick Wigley: Project 3 leader; Roger A. Johns: Project 4 leader; Michael Crow: Project 5 leader; Noah Lechtzin: data management and statistics; Allen Myers: pathology core; Kathleen C. Barnes: genetics/genomics core; Jennifer van Eyk: proteomics core; and Jens Vogel-Claussen: imaging core.

Pulmonary arterial hypertension (PAH) is the leading cause of mortality in patients with the spectrum of scleroderma-related diseases. In addition, recent large clinical trials of PAH suggest that patients with scleroderma-related PAH have increased mortality and a significantly poorer response to therapy compared with patients who have idiopathic PAH. Although the reason for this discrepancy remains unclear, we hypothesized for this SCCOR that the overall worse outcome in scleroderma-related PAH is related to more severe structural changes involving the pulmonary vasculature (PV) and the right ventricle (RV), resulting in marked RV-PV dysfunction. Therefore, this SCCOR project is focused on understanding the complex PV and RV remodeling, resulting RV-PV uncoupling, and their crucial impact on morbidity and mortality in PAH.

In this SCCOR, we use scleroderma-related PAH as a clinical paradigm, contrasting it to idiopathic PAH, because of its particular severity, lack of response to available PAH therapy, and potential underlying genetic factors that dictate outcome. Because of the extensive expertise of our team in molecular and diagnostic pulmonary medicine and cardiology, we have the unique opportunity to not only characterize RV-PV responses in scleroderma-related PAH with increased sensitivity and clarity, but to also identify new molecular targets for potential therapy using state of the art imaging and genomic and proteomic technology. Relying on novel imaging systems and molecular tools, we proposed to conduct rigorous phenotypic characterization of patients who have scleroderma-related PAH. Our focus on animal models provides us with additional candidate genes and proteins for characterization and targeting in human studies.

We have the opportunity to validate the clinical importance of these genes in a large cohort of well-phenotyped patients with PAH, using functional genomics and proteomic approaches with characterization of potentially important polymorphisms. We hope

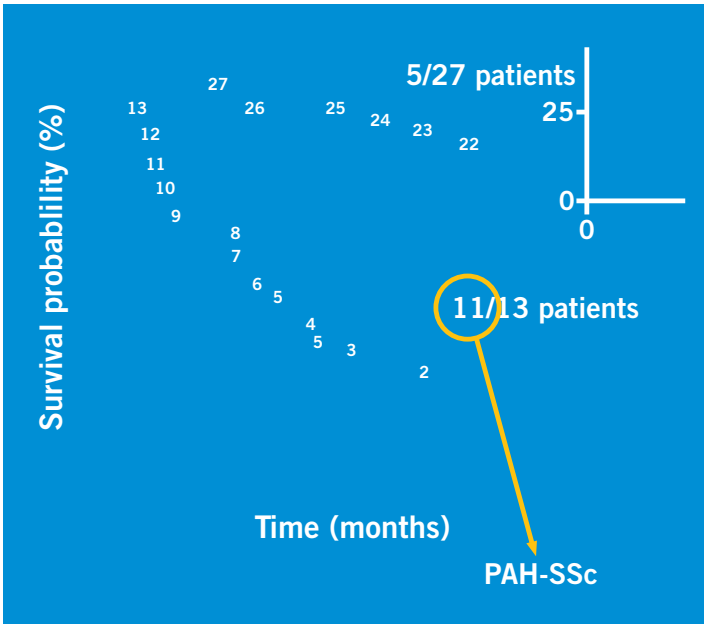

Figure 1. Kaplan and Meier estimates of survival (all-cause mortality) in patients stratified by serum sodium.

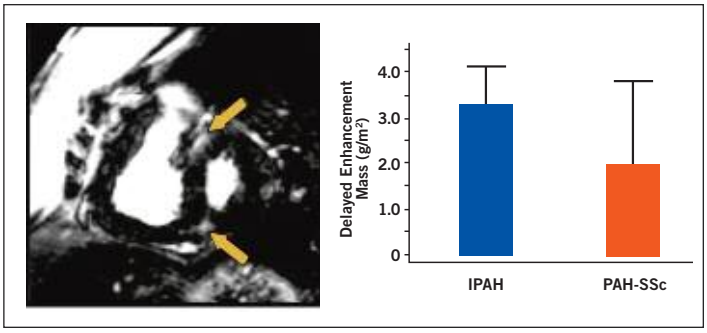

Figure 2. Gadolinium delayed enhancement is seen essentially at RV insertion site. Right graph shows no difference in scar mass between idiopathic PAH and PAH-SS patients.
Note: 11 of 13 patients with hyponatremia who died had scleroderma-related PAH.

that our data will provide new insights into the molecular basis for rational strategies for patients who have scleroderma-related PAH, and elucidate the relationship of RV-PV dysfunction to the activation of pathological gene expression in genetically susceptible patients.

In summary, the Hopkins SCCOR application represents a consortium of investigators with multidisciplinary expertise. The common goal to use state-of-the-art physiological, molecular, and genomic and proteomic approaches as well as novel phenotyping instrumentation that will provide the deepest understanding of the critical pathobiological processes of RV-PV dysfunction and uncoupling to date, and define key genetic determinants relevant to scleroderma-related PAH. The 5 human and animal projects are supported by 6 highly interactive cores (administration, data management/bioinformatics, molecular pathology, genomic and genotyping, proteomics, and imaging). We anticipate our work will provide a foundation for meaningful translational research that will facilitate development of new strategies, uncover therapeutic targets, and define new biomarkers and prognostic indicators that will limit the current dismal outcome of scleroderma-associated PAH.

Progress

The major goals of this SCCOR project are to develop reliable measures of RV-PV function, to characterize patterns of gene expression and identify candidate gene polymorphisms associated with susceptibility to PAH, and to use these tools to guide therapy aimed at RV-PV dysfunction in scleroderma-related PAH. As part of our SCCOR activities, we have recently demonstrated that hyponatremia is a significant indicator of survival (**Figure 1**) in patients with PAH, in particular in patients with scleroderma-related PAH.[1] Hyponatremia is 9 times more likely to be present in scleroderma-related PAH when controlling for hemodynamics and renal function, which suggests that up-regulation of the renine-aldosterone-angiotensin system (RAAS) in response to hemodynamic stress from PAH differs between idiopathic PAH and scleroderma-related PAH. Based on this and other clinical findings that indicate the involvement of RAAS activation in scleroderma-related PAH, some members of our team are focusing their effort on genes pertinent to neurohormonal activation such as adreno-medullin.

Characterizing RV-PV Function

To characterize optimal measures of RV-PV function in scleroderma-related PAH we use a combination of hemodynamic data obtained from right heart catheterization data, echocardiographic parameters, and cardiac MRI with gadolinium imaging and stress test (adenosine infusion). We compare these data to patients with idiopathic PAH. RV function is an important determinant of prognosis in pulmonary hypertension as it is the single most significant prognostic marker of survival. In a prospectively studied cohort of 63 consecutive patients with PH who were referred for a clinically indicated right heart catheterization we demonstrated that the degree of tricuspid annular displacement (tricuspid annular plane systolic excursion or TAPSE) powerfully reflects RV function and prognosis in PAH.[2] Specifically, we demonstrated that a low TAPSE value of less than 1.8 cm was associated with greater RV systolic dysfunction, more RV remodeling, and right ventricle-left ventricle disproportion. More importantly, this study demonstrated that TAPSE could predict survival when these patients were followed over time on therapy. This is now a widely quoted study among the PH community.

In addition, we have focused on several cardiac MRI parameters obtained prospectively and within 2 to 4 hours of right heart catheterization. Pulmonary distensibility is of interest because of the potential of increased fibrosis that can cause stiffening of the proximal pulmonary arteries in scleroderma-related PAH and contribute to RV-PV uncoupling. This analysis has generated some intriguing results comparing scleroderma patients with and without PAH and controls. We have also focused on myocardial scarring in PAH patients and postulated that patients who have scleroderma-related PAH might have increased scar mass compared to patients with idiopathic PAH. Although we found no difference in scar mass between the 2 groups (**Figure 2**), scar mass as assessed by cardiac MRI correlated strongly with RV end diastolic volume in patients with scleroderma-related PAH but not in those with idiopathic PAH (**Table**).

Candidate Genes for Scleroderma-Related PAH

We have published our first observation for the use of genomic profiling in patients with scleroderma-related PAH (compared with patients who have idiopathic PAH). Briefly, we hypothesized that PAH-associated genes identified by expression profiling of peripheral blood mononuclear cells from patients with idiopathic PAH can also be identified in peripheral blood mononuclear cells

Table. Correlation of Hemodynamic and MRI Morphology Variables With Scar Mass in Scleroderma-Related PAH

	r	P
Right ventricular ejection fraction	–0.391	NS
Right ventricular end diastolic mass index	0.729	NS
Right ventricular end diastolic volume index	0.970	.0014
Mean pulmonary artery pressure	0.600	NS
Pulmonary vascular resistance	0.682	NS
Cardiac index	–0.294	NS

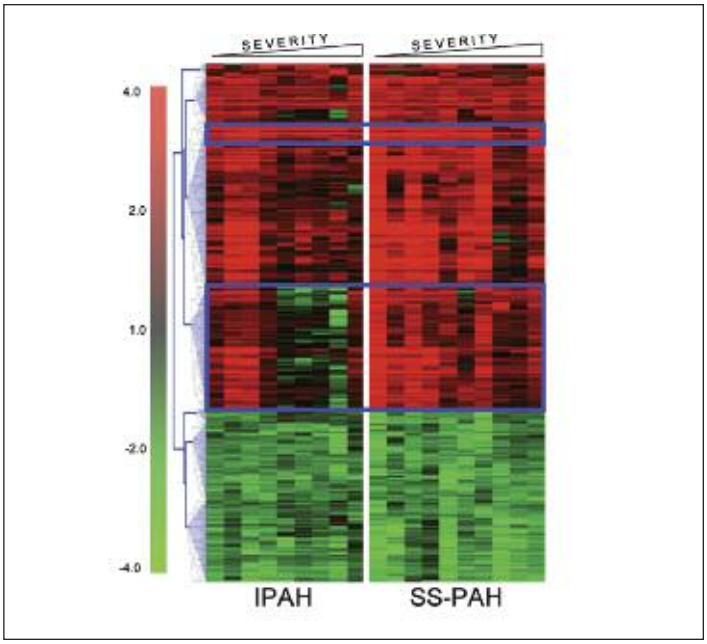

Figure 3. Color display of genes discriminating between idiopathic PAH and PAH-SS versus controls and assorted according to disease severity. Red, increased expression versus control; green, lower expression.

from scleroderma-related PAH. Gene expression profiles of peripheral blood mononuclear cells collected from patients with idiopathic PAH, those with scleroderma-related PAH, and healthy controls were generated using HG_U133A_2.0 GeneChips. Disease severity in consecutive patients was assessed by functional status and hemodynamic measurements. As shown in **Figure 3**, there were many genes that were up- or down-regulated concordantly or not in the 2 groups. Our data demonstrate that peripheral blood mononuclear cells from patients with scleroderma-related PAH carry distinct transcriptional expression.[3] Deciphering the role of genes involved in vascular remodeling and PAH de-

velopment may reveal novel targets for treatment for this devastating disorder, which is one of the most important goals of this SCCOR project.

Biological Validation

To establish biological validation of high-risk alleles in selected PAH candidate genes via mid- and high-throughput genotyping in a large cohort of scleroderma-related PAH patients we have collected over 1400 DNA samples (mostly patients with scleroderma of whom 10% have scleroderma-related PAH). We used these samples for further DNA analysis and to identify single nucleotide polymorphisms of candidate genes identified in our SCCOR projects dedicated to human and animal studies. We have also established collaborations with other investigators from the PH community to share additional DNA samples. We will begin high throughput genotyping as early as December 1, 2008. The goal is to perform wide-scale single nucleotide polymorphisms analysis on several candidate genes (from a current total list of 39 genes).

Conclusion

We continue to gain significant momentum and synergy with other SCCOR investigators and have moved all aspects of our project forward. We anticipate that the coming year will be, like this past year, extremely productive now that we have most of our techniques and analytical tools in place. More importantly, we hope that our efforts will help clarify the pathobiology underlying scleroderma-related PAH and its current poor outcome and identify new molecular targets for the design of targeted therapies.

References

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