ATS

2023 Grover Conference

PROGRAM

Precision Medicine For Pulmonary Vascular Disease: *The Future is Now*

ATS 2023 Grover Conference

Precision Medicine For Pulmonary Vascular Disease: *The Future is Now*

The American Thoracic Society and the conference organizing committee gratefully acknowledge the support of this conference by:

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- **The Cardiovascular Medical Research and Education Fund**

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2023 GROVER CONFERENCE
Precision Medicine for Pulmonary Vascular Disease: *The Future is Now*

THE PROGRAM

About the Program

Since its inauguration in 1984, the 2023 Grover Conference will be the 20th in this series, representing the longest-standing conference on Pulmonary Circulation. Today it remains the principal conference for pulmonary vascular function, directly related to the interests of the ATS. Relatively small groups of attendees and highly focused topics facilitate maximal contact for scientific discourse. The seclusion of the Conference Center in Tabernash, CO provides the best opportunity for undisturbed exchange of ideas at both formal sessions and informal meetings at the conference center. The meeting is open to all interested scientists and clinician-scientists. As with past Conferences, this Conference will consist of a productive mix of young and senior scientists. Although the total number of participants is limited, we anticipate that the overall conference participants, including speakers and attendees, will be diverse and involve participants drawn from many ATS Assemblies.

Program Objectives

Precision medicine is an approach to disease treatment that takes into account individual variability in genes, environment, and lifestyle to identify clinical phenotypes that would benefit from targeted and highly effective therapies. The importance of precision medicine to the future of US health care is based on the potential capacity to provide practitioners with a way to integrate seemingly disparate data points (e.g., genetics, proteomics, epigenetics, metabolomics, medical record data, etc.) into a platform that can lead to improved clinical outcomes, health care costs and quality of health care.

Given the growing advances in our understanding of the pathobiology and management of pulmonary vascular disorders such as pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH), the time is ripe to discuss how a precision medicine strategy could help facilitate the translation of scientific discoveries into clinical tools (e.g. biomarkers, prediction algorithms, clinical trial design, drug discovery, etc.) that can help improve our capacity to properly diagnose and design the optimal treatment strategy for these patients.

This Grover conference will go beyond pulmonary arterial hypertension genetics (the focus of the 2015 Grover Conference) to address how a precision medicine-based approach can help us understand the pathobiology of pulmonary vascular disorders, identify novel treatment paradigms and the technical and bioethical issues that need to be addressed towards making this the standard of care for patients with pulmonary vascular diseases.

THE PROGRAM

Learning Objectives

At the conclusion of this program, the learner will be able to:

1. Recognize what precision medicine is and how it can improve diagnosis and treatment of pulmonary vascular disorders.
2. Understand the state-of-the-art knowledge concerning clinical aspects and pathophysiology of pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) and how precision medicine could help address current gaps.
3. Understand the current state of the fields of genomics, proteomics, metabolomics and epigenetics in PAH and CTEPH and how data can be integrated into a comprehensive tool for drug and biomarker discovery.
4. Discuss technological advances in gene sequencing, deep cell phenotyping, humanized animal models and organ-on-a-chip strategies.
5. Discuss how precision medicine can improve the current design and outcome analysis of clinical trials in PAH and CTEPH.
6. Recognize the role of medical record and bioethics in implementing precision medicine in the clinic, when individualizing care of patients and sharing information with caregivers and other professionals.

Who Should Attend

Clinicians and scientists who focus on pulmonary vascular disorders as well as postdoctoral fellows seeking training in basic and clinical pulmonary vascular research. We anticipate that the conference will also attract medical professionals, representatives from pharmaceutical and biotechnology companies, and scientists from related fields who are interested in application of precision medicine to cardiopulmonary disorders.

Save the Date

ATS 2024

May 17 - 22

2023 GROVER CONFERENCE
Precision Medicine for Pulmonary Vascular Disease: *The Future is Now*

COURSE SCHEDULE

Monday, October 16, 2023

12:00 pm ARRIVALS

6:00 pm WELCOME RECEPTION AND DINNER

7:00 pm **State of the Art Lecture:**
Beyond Genotype and Phenotype: Has Omics Changed Pulmonary Medicine?
Naftali Kaminski, MD, ATSF, Yale School of Medicine

Tuesday, October 17, 2023

SESSION I

Clinical Phenotypes Of Pulmonary Vascular Disorders -
What We Know And What We Don't Know

Moderators:
Katherine R. Clapham, MD, University of Utah | Olga Rafikova, MD, PhD, Indiana University

7-8:00 am BREAKFAST

8:05 am **Welcome and Introduction**
Anna Hemnes, MD, ATSF, Vanderbilt University | Vinicio de Jesus Perez, MD, ATSF, Stanford University | Prof. Martin Wilkins, Imperial College of London

8:15 am ***Pulmonary Arterial Hypertension: One disease, Different Phenotypes***
Bradley Maron, MD, BWH

8:45 am ***The Continuum of Vascular Remodeling in Heart Failure***
Marc Simon, MD, MS, UCSF

9:15 am ***Comorbidity-Driven Taxonomy of Pediatric Pulmonary Hypertension***
Rachel K. Hopper, MD, Stanford University

9:45 am BREAK (10 min)

9:55 am ***Pulmonary Embolism And CTEPH: One Disease with Different Phenotypes?***
Gustavo A. Heresi, MD, MSci, Cleveland Clinic

Tuesday, October 17, 2023

10:25 am *ALI, ARDS, and Bronchopulmonary Dysplasia: A Spectrum Of Phenotypes*
Rebecca F. Hough, MD, PhD, Columbia University

10:55 am *John T. Reeves Memorial Lecture: Pulmonary Vascular Disorders Related to Scleroderma And Connective Tissue Diseases: Is Autoimmunity the Only Phenotype?*
Paul M. Hassoun, MD, Johns Hopkins

11:25 am **Open Discussion**

12:00 pm **LUNCH**

SESSION II

Genetics of Pulmonary Vascular Disorders: From Family Studies to Population Studies

Moderators:
Sasha Z. Prisco, MD, PhD, University of Minnesota
Jair Antonio Tenorio, MSc, PhD, Institute of Medical and Molecular Geneticist

3:00 pm *Diagnosis and Management of Genetic Diseases in the Era of Next Generation Sequencing*
Jair Antonio Tenorio, MSc, PhD, Institute of Medical and Molecular Geneticist

3:30 pm *Genetics of PAH*
Stefan Graf, PhD, University of Cambridge Medicine

4:00 pm *Next Steps for the UK Cohort Study*
Allan Lawrie, PhD, Imperial College London

4:30 pm *Unlocking the Potential-Novel Insights in Smooth Muscle Cells and Fibroblasts Heterogeneity*
Grazyna Kwapiszewska-Marsh, DrMed, Ludwig Boltzmann Institute for Lung Vascular Research

5:00 pm **Open Discussion**

5:15 pm **Abstract Presentation:**
ATP Citrate Lyase (ACLY): a Promising Target Against Vascular Remodeling Development
Yann Grobs, MSc, Laval University ULAVAL, Department of Medicine

5:30 pm **Abstract Presentation:**
Hypusine Signaling: A Novel Pathway Driving Vascular Remodeling in Pulmonary Arterial Hypertension
Sarah-Eve Lemay, MSc, Laval University ULAVAL, Department of Medicine

6:00 pm **DINNER**

8:00 pm *Career Development Session: How to Obtain your First Job in Academia or Industry*
Julie Bastarache, MD, Vanderbilt University
Olga Rafikova, MD, PhD, Indiana University

Wednesday, October 18, 2023

SESSION III

Biomarker Discovery and Cell Therapy for Pulmonary Vascular Disorders in the Era of Precision Medicine

Moderators:

James R. Klinger, MD, ATSF, Rhode Island Hospital | William M. Oldham, MD, PhD, Harvard University

7-8:00 am **BREAKFAST**

8:05 am ***Epigenetics, Metabolomics And Proteomics As Tools For Precision Medicine In Pulmonary Vascular Medicine***
Stefan Gräf, PhD, University of Cambridge Medicine

8:35 am ***Using Platform Omic Technologies to Probe Blood in Pulmonary Vascular Disease***
Christopher J. Rhodes, PhD, Imperial College London

9:05 am ***Proteomics and Machine Learning for Discovery of Biomarkers in Pulmonary Vascular Disorders***
Andrew J. Sweatt, MD, Stanford University

9:35 am ***Exosomes and Microparticles: Biomarkers, Therapeutic Vectors or Both?***
Natalie N. Bauer, PhD, University of South Alabama

10:05 am **BREAK (10 min)**

10:15 am ***Single Cell 'Omics, Circulating Cells And Genetic Engineering To Accelerate Biomarker Discovery And Cell Therapy***
Duncan J. Stewart, MD, Ottawa Hospital Research Institute

10:45 am ***Novel Sub-populations of Lung Capillary Endothelial Cells and Their Functional Significance***
Ruslan Rafikov, PhD, University of Arizona

11:05 am ***Robyn J. Barst Memorial Lecture: Bronchopulmonary Dysplasia and ALI/ARDS In Pediatrics: New Biomarkers and Role of Cell Therapy***
Kara N. Goss, MD, University of Texas Southwestern Medicine

11:35 am ***Abstract Presentation: Association Of Right Ventricular Diastolic Stiffness and RV Ejection Fraction with Mortality In Patients With Pulmonary Hypertension***
Rebecca R. Vanderpool, PhD, Ohio State University

12:00 pm **LUNCH**

SESSION IV

From Precision Biology to Clinical Trials: Examples for how Basic Research Accelerates Clinical Trials in Pulmonary Vascular Diseases

Moderators:
Ke Yuan, PhD, Boston Children's Hospital | Corey E. Ventetuolo, MD, MS, Brown

3:00 pm ***Sotatercept for Treatment of PAH: The PULSAR and STELLAR Data (15')***
David B. Badesch, MD, University of Colorado

3:40 pm ***Biological Role of Tyrosine Kinase receptors in PAH (15')***
Bradley Maron, MD, BWH

Positioning Imatinib for PAH (PIPAH study) (15')
Prof. Martin Wilkins, Imperial College London

4:20 pm ***Rituximab for Scleroderma-PAH Targeting B Cells in PAH***
Mark Nicolls, MD, Stanford

Clinical trial of Rituximab in PAH (15')
Roham T. Zamanian, MD, FCCP, Stanford University

5:00 pm ***Targeting Bromodomain proteins with Apabetalone Bromodomain Protein Biology and rationale for therapy (15')***
Sebastien Bonnet, PhD, MSc, Institute of Cardiology & Pulmonary of Quebec

6:00 pm **DINNER**

8:00 pm **After Dinner Talk: Estelle B. Grover Memorial Lecture**
The "Interactome" and the Repurposing of Medicines for cardiopulmonary Diseases: Big Data in Precision Medicine
Stephen Y. Chan, MD, PhD, University of Pittsburgh

Thursday, October 19, 2023

SESSION V

The Right Ventricle: A Phenotype of its Own

Moderators:
Rebecca R. Vanderpool, PhD, Ohio State | Roberto Bernando, MD, MS, OU College of Medicine

7-8:00 am **BREAKFAST**

8:05 am ***Deep-Phenotyping the Heart***
Kurt Prins, MD, PhD, University of Minnesota

8:35 am ***Genomic And Proteomic Studies in the RV: Therapeutic Possibilities***
Tim Lahm, MD, ATSF, University of Colorado

9:05 am ***Metabolomics of The RV: What We have Learned and What We Need to Know***
Jane Leopold, MD, BWH

9:35 am ***The Transition from Acute to Chronic PE – Insights from Single Cell RNA Sequencing***
Sudarshan Rajagopal, MD, PhD, Duke

10:05 am **BREAK (10 min)**

10:15 am ***Cardiac Imaging, Radiometrics and their Role in Precision Medicine***
Harm J. Bogaard, MD, PhD, Amsterdam UMC

10:45 am ***Intravascular Hidden Threats: Reshaping the Pulmonary Vasculature and the Right Ventricle***
Suellen D'Arc Dos Santos Oliveira, PhD, Msci, University of Illinois at Chicago

11:15 am ***Cluster Analysis to Define Right Heart Failure Phenotypes in Pulmonary Vascular Diseases***
Rebecca R. Vanderpool, PhD, Ohio State University

11:45 am **Abstract Presentation:**
Pathogenic Role for RUNX1 in Pulmonary Arterial Hypertension
James R. Klinger, MD, ATSFr, Rhode Island Hospital

12:00 pm **LUNCH**

SESSION VI

Understanding epigenetics and their role in Precision Medicine: A New Frontier?

Moderators:
Tatiana Kudryashova, PhD, UC Davis | Grazyna Kwapiszewska-Marsh, DrMed, ILH of JLU

3:00 pm **Terry Wagner Memorial Lecture:**
Epigenetics for Gene Discovery and Phenotyping of Pulmonary Vascular Disorders
Kurt R. Stenmark, MD, University of Colorado Denver

3:30 pm ***HIF and Epigenetics in the Pathogenesis of PAH***
Zhiyu Dai, PhD, University of Arizona

4:00 pm ***Beyond the Coding Regions: Microrna, Lncrna and Control of Non-Coding RNA Expression And Function***
Ke Yuan, PhD, Harvard University

4:30 pm ***Epigenetics and COVID in PVD***
Harry Karmouty-Quintana, PhD, McGovern Medical School at UT Health

5:00 pm **Abstract Presentation:**
Lactobacillus Suppresses Glycoprotein-130-Mediated Microtubule Remodeling to Support Right Ventricular Function in Pulmonary Arterial Hypertension
Sasha Z. Prisco, MD, PhD, University of Minnesota

5:30 pm ***Cancer, Epigenetics, and Pulmonary Hypertension: Translational Opportunities***
Sebastian Bonnet, PhD, MSc, Institute of Cardiology & Pulmonary of Quebec

6:00 pm **DINNER**

7:00 pm **Poster Session chaired by Drs. Elena Goncharova, Andrew Bryant, and Suellen D'Arc Oliveira. Poster presenters to give short summaries of their research followed by questions from the audience.**

Friday, October 20, 2023

SESSION VII

Integrating Precision Medicine to Clinical Care

Moderators:
Peter Leary, MD, PhD, UW Medical Center | Vineet Agrawal, MD, Vanderbilt

7-8:00 am **BREAKFAST**

8:05 am ***Overview of Methamphetamine Induced Pulmonary Hypertension***
Katherine R. Clapham, MD University of Utah

8:35 am ***Hemodynamics And Vasoreactivity - Can they Help us Phenotype PAH Patients?- YES***
Roham Zamanian, MD, FCCP, Stanford University

8:45 am ***Hemodynamics And Vasoreactivity - Can they Help us Phenotype PAH Patients?- NO***
Brian Houston, MD, FACC, MUSC

8:55 am **Rebuttals and discussion**

9:05 am ***The Discovery of Sotatercept and the Future of Drug Discovery on PH***
Paul B. Yu, MD, PhD, Harvard University

9:35 am **BREAK (10 min)**

9:45 am ***Using Wearables to Monitor Patients with Pulmonary Vascular Diseases***
Raymond L. Benza, MD, Ohio State Medical Center

10:15 am ***Ethical Issues Surrounding Precision Medicine***
Daphne O. Martschenko, BA, MPhil, PhD, Stanford University

10:45 am ***Role of a Comprehensive Electronic Medical Record in Precision Medicine- What is Needed***
Evan Brittain, MD, Vanderbilt University

11:15 pm **Closing Summary**
Anna Hemnes, MD, ATSF, Vanderbilt University
Vinicio de Jesus Perez, MD, ATSF, Stanford University
Prof. Martin Wilkins, Imperial College of London

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- **The National Institutes of Health – National Heart, Lung, and Blood Institute**

cAMP enriched EVs improve hypoxic pulmonary hypertension.

A. Bhadra[1], J. L. Hewes[1,2], C. Zhou[2,3], J. Lee[2,4], N. N. Bauer[1,2].

[1]Pharmacology, University of South Alabama College of Medicine, [2]Center for Lung Biology, University of South Alabama College of Medicine, [3]Physiology and Cell Biology, University of South Alabama College of Medicine, [4]Physiology and Cell Biology, Internal Medicine, University of South Alabama College of Medicine, Mobile, AL, United States

Extracellular vesicles (EVs) play a role in pulmonary vascular cell – cell communication and pulmonary hypertension. Our lab reported the novel finding that stimulation of pulmonary endothelial cells with a beta agonist and a phosphodiesterase inhibitor induced enrichment of cyclic adenosine monophosphate (cAMP) in EVs. cAMP protects the pulmonary vasculature by regulation of permeability, vasoreactivity and proliferation. Extracellular vesicles provide a protected environment for circulating cAMP. Thus, we hypothesized that administration of cAMP, in the protected environment of an EV, could deliver cAMP to improve outcomes in pulmonary hypertension. Briefly, male Sprague Dawley rats, maintained in normoxic or hypoxic conditions for 3 weeks, received 50 ug of cAMP-enriched EVs (cAMP-EVs) per day over 3 days via tail vein injection. cAMP-EV injections improved the Fulton index (non-injected hypoxia rat 0.37 ± 0.039 versus injected hypoxia rat 0.32 ± 0.019, p value 0.032 n = 5) and echocardiography revealed PH rats that received cAMP-EVs had a significant increase in PAAT/PAET ratio compared to those that did not (non-injected hypoxia rat 0.27 ± 0.056 versus injected hypoxia rat 0.32 ± 0.04, p value 0.04, n = 6). Using IVIS analysis of isolated tissues to detect PKH-labeled EVs we found that cAMP-enriched EVs accumulated in the lung but were not detectable in the heart. To confirm this was not strictly a vasoreactivity effect, we also examined PCNA, a marker of proliferation, in histological sections and found it was decreased in the presence of cAMP-EVs. Pulmonary arterial thickness was also significantly improved in the presence of cAMP-EVs. Combined these data suggest that cAMP-EVs may decrease right ventricular hypertrophy, improve pulmonary arterial function, and repair hypoxic vascular injury. Future investigations will determine whether the observed response is cAMP dependent and further evaluate the specificity of pulmonary vascular uptake of cAMP-EVs.

Lung capillary endothelium to arterial endothelium transition in pulmonary arterial hypertension.

Bin Liu[1,2,3], Dan Yi[1,2,3], Xiaomei Xia[1,2], Karina Ramirez[1,2], Ryan Dong[1,2], Hongxu Ding[4], Vladimir Kalinichenko[5], Michael B. Fallon[2], Zhiyu Dai[1,2,3].

[1]Division of Pulmonary, Critical Care and Sleep, [2]Department of Internal Medicine, College of Medicine-Phoenix, University of Arizona, Phoenix, Arizona, USA, [3]Translational Cardiovascular Research Center, College of Medicine-Phoenix, University of Arizona, Phoenix, Arizona, USA, [4]Department of Pharmacy Practice & Science, College of Pharmacy, University of Arizona, Tucson, Arizona, USA, [5]Phoenix Children's Health Research Institute, College of Medicine-Phoenix, University of Arizona, Phoenix, Arizona, USA

Abstract: Pulmonary arterial hypertension (PAH) is characterized by a progressive increase of pulmonary vascular resistance and obliterative pulmonary vascular remodeling that result in right heart hypertrophy, failure, and premature death. The underlying mechanisms of loss of distal capillary endothelial cells (ECs) and obliterative vascular lesion formation remain unclear. Our recent single-cell RNA sequencing, spatial transcriptomics analysis, RNASCOPE, and immunostaining analysis showed that arterial ECs accumulation and loss of capillary ECs were evident in human PAH patients and pulmonary hypertension (PH) rodents. Pseudotime trajectory analysis of the single-cell RNA sequencing data suggest that lung capillary ECs transit to arterial ECs during the development of PH. Our study also identified CXCL12 as the marker for arterial ECs in PH. General capillary EC lineage tracing approach using Plvap-DreERT2; Tdtomato mice demonstrated that general capillary ECs gave rise to arterial ECs during PH development. Genetic deletion of HIF-2a or pharmacological inhibition of mediator kinase Cdk19 normalized the arterial programming in PH. In conclusion, our study demonstrates that general capillary endothelium transits to arterial endothelium through the HIF-2a-Cdk19 pathway during the development of PAH. Thus, targeting arterial EC transition might be a novel approach for treating PAH patients.

Fatty acid-binding proteins contribute to the pathogenesis of pulmonary hypertension.

Bin Liu[1,2,3], Dan Yi[1,2,3], Karina Ramirez[1,2], Xiaomei Xia[1,2], Ruslan Rafikov[4], Sebastian Bonnet[5], Michael B. Fallon[2], and Olivier Boucherat[5], Zhiyu Dai[1,2,3]*.

[1]Division of Pulmonary, Critical Care and Sleep, [2]Department of Internal Medicine, College of Medicine-Phoenix, University of Arizona, Phoenix, Arizona, USA, [3]Translational Cardiovascular Research Center, College of Medicine-Phoenix, University of Arizona, Phoenix, Arizona, USA, [4]Department of Medicine, University of Arizona College of Medicine, Tucson, Arizona, [5]Pulmonary Hypertension and Vascular Biology Research Group, Faculty of Medicine, Laval University, Quebec, QC, Canada

Introduction: Pulmonary arterial hypertension (PAH) is a disaster disease characterized by obliterative vascular remodeling and persistent increase of vascular resistance, leading to right heart failure and premature death. Understanding the cellular and molecular mechanisms will help develop novel therapeutic approaches for PAH patients.

Hypothesis: We hypothesis that endothelial fatty acid metabolism is critical for obstructive vascular remodeling in the pathogenesis of PAH.

Methods: A severe mouse model of PH *Egln1*^{Tie2Cre} mice were bred with *Fabp45*$^{-/-}$ mice to generate *Egln1*^{Tie2Cre}/*Fabp45*$^{-/-}$ mice. Single-cell RNA sequencing (scRNA-seq) analysis and metabolomic analysis were used to profile the pulmonary cells in Egln1Tie2Cre mice and *Egln1*^{Tie2Cre}/*Fabp45*$^{-/-}$ mice. Human hPAEC from idiopathic PAH patients and healthy donors, monocrotaline (MCT)-induced and *Sugen5416*/hypoxia (SuHx)-induced PH rats were used to measure fatty acid-binding protein 4 and 5 (FABP4 and FABP5) expression. siRNA mediated knockdown of FABP4 and FABP5 and lentivirus mediated FABP4 and 5 overexpression were performed to study cell proliferation, apoptosis, glycolysis, fatty acid oxidation. Echocardiography, hemodynamics, histological and immunostaining assay were performed to evaluate the PH phenotypes.

Results: Both FABP4 and 5 were highly induced in the ECs of *Egln1*^{Tie2Cre} mice and PAECs from IPAH patients, as well as the whole lungs of MCT and SuHx-induced PH rats. Knockdown or overexpression of *FABP4-5* reduced or enhanced EC proliferation, starvation-induced Caspase 3/7 activity, glycolysis and fatty acid oxidation. Genetic deletion of *Fabp4* and *5* in *Egln1*^{Tie2Cre} mice exhibited a reduction of right ventricular systolic pressure (RVSP), RV hypertrophy, and attenuation of pulmonary vascular remodeling, prevention of right heart failure. Fabp4-5 deletion also normalized EC glycolysis and arterial gene programming, reduced HIF-2a expression and endothelial proliferation in *Egln1*^{Tie2Cre} mice.

Conclusions: FABP4 and 5 control EC glycolysis and arterial programming and contribute to the development of severe PH.

Defining Right Ventricular Energy Metabolism in Pulmonary Arterial Hypertension Using Hyperpolarized ^{13}C MRI.

Jae Mo Park, Gregory P Barton, Sung-Han Lin, Craig R Malloy, Kara N Goss.

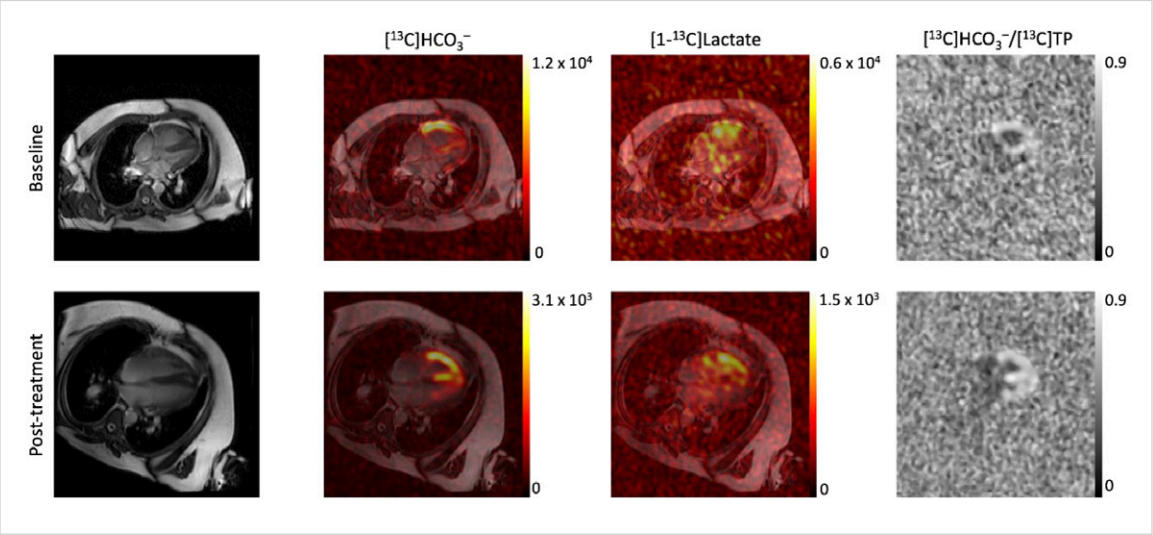
UT Southwestern Medical Center, Dallas, Texas

Background: Right ventricular (RV) failure in pulmonary arterial hypertension (PAH) significantly increases mortality risk. Preclinical studies suggest this is accompanied by an increasing rate of RV myocardial glucose utilization, particularly glycolysis, though this has been difficult to quantify in humans due to limitations of imaging the RV. 13C MRI using hyperpolarized (HP) [1-^{13}C]pyruvate is a novel modality to track the metabolic fate of pyruvate by assessing its products such as lactate (glycolysis) and bicarbonate (glucose oxidation) that may provide novel insights into the failing RV.

Methods: In this proof-of-concept pilot study (NCT04968210), 3 participants with newly diagnosed group 1 PAH will complete HP ^{13}C-pyruvate MRI at baseline and again 4-6 months after initiation of pulmonary vasodilator therapy. At each visit, HP [1-^{13}C]pyruvate is prepared using a SPINlab DNP polarizer and administered intravenously during a ^{13}C/1H-integrated MRI session. Metabolite maps of HP [^{13}C]bicarbonate, [1-^{13}C]lactate, and [1-^{13}C]pyruvate are dynamically acquired every cardiac cycle in an interleaved manner by exciting one metabolite at a time. 1H cardiac cine MRI are acquired for cardiac function, and clinical characteristics extracted from the medical record.

Results: To date, a 62 year old male with PAH has completed the study. After initiation of oral vasodilators, cardiac function and hemodynamics improved significantly: mPAP 56 to 45 mmHg, cardiac index 2.2 to 3.0 L/min/m2, PVR 11.9 to 7.1 Wood units. Pyruvate oxidation, measured by time-averaged bicarbonate/total products (TP), increased by 7.8% in RV free wall, 11.1% in LV free wall, and 9.7% in septum.

Conclusions: The failing RV can be metabolically imaged using HP ^{13}C MRI. How RV metabolism modulates RV function merits further study.



Organ-specific pericyte markers and identities by scRNAseq analysis.

Seung-Han Baek, Ke Yuan*.

Division of Pulmonary Medicine, Department of Pediatrics, Boston Children's Hospital, Harvard Medical School, Boston, MA 02115
** Presenting author*

Background: Pericytes are mesenchymal-derived mural cells that wrap around capillaries and directly contact endothelial cells. Present throughout the body, including the cardiovascular system, pericytes are proposed to have multipotent cell-like properties and are involved in numerous biological processes, including regulation of vascular development, maturation, permeability, and homeostasis. Despite their physiological importance, the functional heterogeneity, differentiation process, and pathological roles of pericytes still need to be clearly understood, partly due to the inability to reliably distinguish them from other mural cell populations.

Results: Our study focused on identifying pericyte-specific markers by analyzing single- cell RNA sequencing data from tissue-specific mouse pericyte populations generated by the Tabula Muris consortium. Applying either of two known pericyte markers, *Cspg4* or *Pdgfrb* to identify mural clusters, we further defined pericytes as those cells that co- express both

markers but exclude canonical markers for other stromal cells. Single-cell differential expression gene analysis compared this subset with other clusters that identified potential pericyte marker candidates, including *Kcnk3* (in the lung); *Rgs4* (in the heart); *Myh11* and *Kcna5* (in the kidney); *Pcp4l1* (in the bladder); and *Higd1b* (in lung and heart). In addition, we identified novel markers of tissue-specific pericytes and signaling pathways that may be involved in maintaining their identity. Moreover, the identified markers were further validated in Human Lung Cell Atlas and human heart single-cell RNAseq databases. Intriguingly, we found that markers of heart and lung pericytes in mice were conserved in human heart and lung pericytes.

Conclusion: In this study, we, for the first time, identify tissue-specific pericyte markers among lung, heart, kidney and bladder and reveal differentially expressed genes and functional relationships between mural cells.

Association of right ventricular diastolic stiffness and RV ejection fraction with mortality in patients with pulmonary hypertension.

Authors: Alexandra Janowski, Raymond L. Benza, David Kiely, Andrew Swift, Scott Visovatti, and Rebecca R. Vanderpool.

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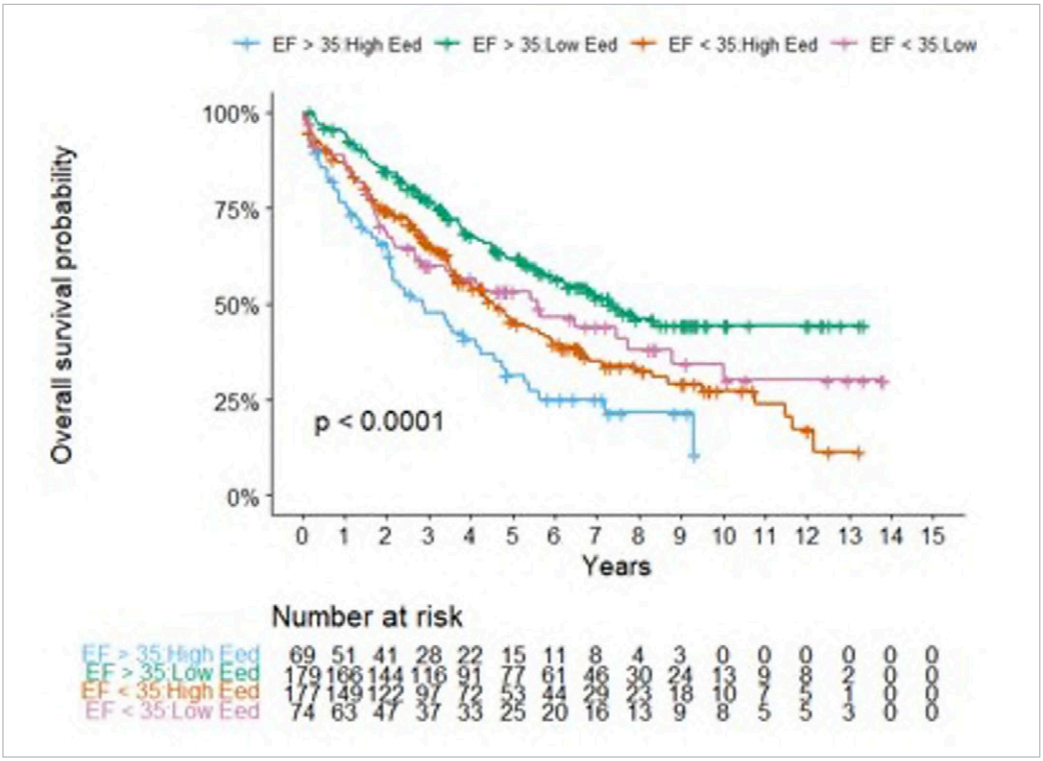
The aim of this study was to investigate associations between RV diastolic stiffness and RV ejection fraction and mortality in patients with PAH. Patients with a baseline RHC and CMR volumes were identified from the UK ASPIRE registry. RV diastolic stiffness (β) was calculated using P=α(eβV-1), a fitting constant (α), right atrial pressure (RAP), end-systolic (ESV) and end- diastolic (EDV) volumes. Arterial afterload (Ea) was estimated as the ratio of end-systolic pressure to stroke volume. Follow-up time was defined as time between the CMR date and death. In participants with CMR and RHC data (n = 499, age: 60±15 yrs, and 77.2% female), median follow-up time was 3.35[1.57-6.11] yrs. Participants were split into high/low End-diastolic elastance (Eed) based on the median 0.35[0.17-0.59] mmHg/ml. High Eed group had elevated PVR (998 ± 462 vs 552 ± 350 dyn·s·cm−5) and Ea (1.59±0.77 vs 1.08±0.53 mmHg/ml) compared to low Eed group. From CMR imaging, High Eed group had decreased LVEF (51±10 vs 56±9%) and RVEF (30±10 vs 42±11%) compared to low Eed group. Age, body surface area, RVEF, mean RAP and Eed associated with mortality. Irrespective of Eed, participants with an RVEF<35% had similar survival rates (Eed>0.35: 86.3% and Eed<0.35: 88.9%). As expected, participants with an RVEF>35% and an Eed<0.35 had a high survival rate (94.9%). Participants with an RVEF>35% and an Eed>0.35 (n = 69, 89.9%% female) had the lowest 1-year survival rate at 76.4%. Elevated RV diastolic stiffness might be a contributing factor to decreased survival in participants with preserved RV function.

Relevant Figures:



Lactobacillus Suppresses Glycoprotein-130-Mediated Microtubule Remodeling to Support Right Ventricular Function in Pulmonary Arterial Hypertension.

Sasha Z. Prisco, MD, PhD, Madelyn Blake, Neal Vogel, MS, Felipe Kazmirczak, MD, E. Kenneth Weir, MD, Thenappan Thenappan, MD, and Kurt W. Prins, MD, PhD.

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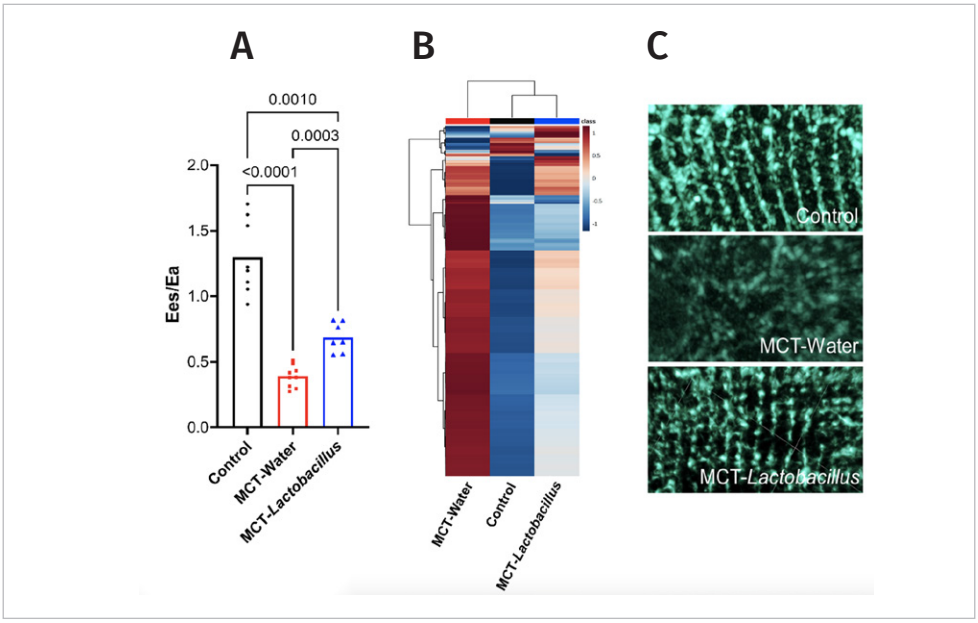
Introduction: Microtubules (MTs) are crucial for cardiomyocyte function as they regulate t-tubule structure, nuclear morphology, and gap junction protein localization. Glycoprotein-130 (GP130) signaling promotes pathological MT remodeling and right ventricular (RV) dysfunction in pulmonary arterial hypertension (PAH), but the trigger for the inflammation-MT connection is unknown. Microbiome dysbiosis activates systemic inflammation, and levels of the anti-inflammatory bacteria Lactobacillus are associated with RV function in rodents. However, the direct effects of *Lactobacillus* on GP130 signaling, MT remodeling, and RV function in PAH are unknown.

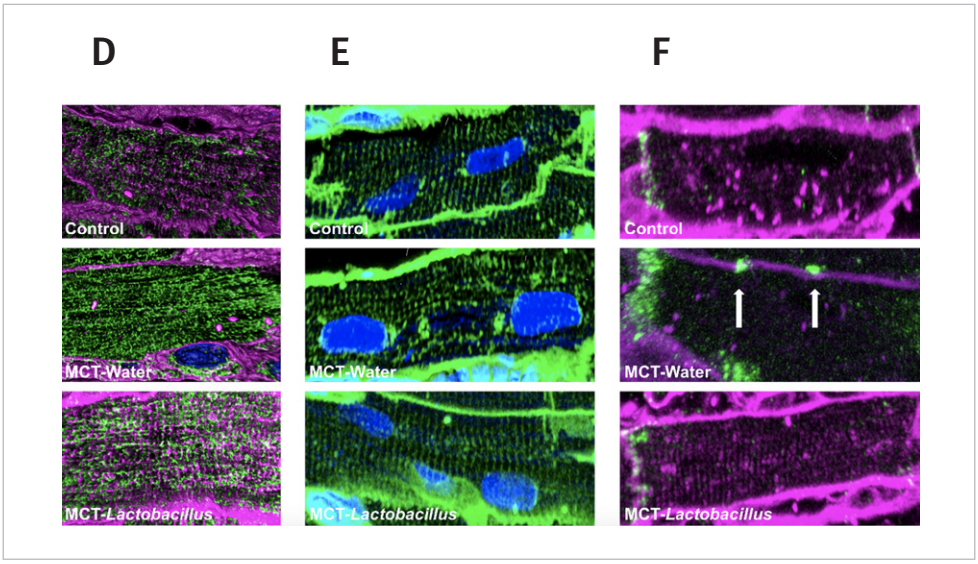
Methods: Rats were randomly allocated into three groups: control, MCT-water, and MCT rats given *Lactobacillus* (MCT-Lactobacillus). Echocardiography and pressure-volume loops defined RV function. Next-generation sequencing evaluated the composition of the bacterial components of the fecal microbiome. SomaScan proteomics quantified the

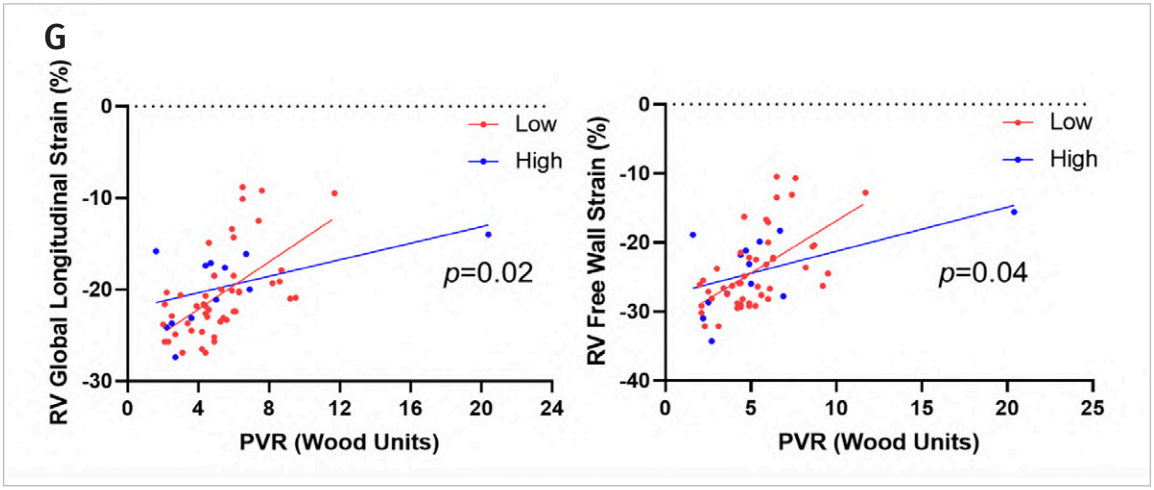
serum proteome. RV and jejunal morphology were assessed with light and super resolution confocal microscopy. The relationship between *Lactobacillus* abundance and RV response to afterload was assessed in 65 PAH patients.

Results: *Lactobacillus* augmented RV function (A) and reduced RV hypertrophy and fibrosis without altering PAH severity. *Lactobacillus* shifted the serum proteomic signature towards control (B) and reduced circulating GP130 ligands, normalized RV t-tubule architecture (C), MT density (D), and nucleus size (E), and prevented connexin-43 lateralization in RV cardiomyocytes (F). *Lactobacillus* restructured the microbiome, and concomitantly improved jejunal epithelial cell morphology with increased villus/microvillus length and glycocalyx thickness. PAH patients with fecal *Lactobacillus* had superior RV adaptation as afterload increased (G).

Conclusion: *Lactobacillus* combats GP130-mediated MT remodeling to support RV function.







Pathogenic Role for RUNX1 in Pulmonary Arterial Hypertension.

James R. Klinger[1], Euy-Myoung Jeong[2], Mandy Pereira[1,2], Olin D. Liang2.

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Previously, we showed that Runx1 expression is increased in circulating CD34+CD133+ progenitor cells in patients with pulmonary arterial hypertension (PAH) and that deletion of Runx1 either in adult endothelium of Cdh5-CreERT2;Runx1(flox/flox) mice or in cells of myeloid lineage in LysM-Cre;Runx1(flox/flox) mice prevented PH induced by VEGF-receptor antagonist Sugen 5416 and hypoxia (SuHx-PH). In addition, the RUNX1 inhibitor Ro5-3335 prevented and reversed established SuHx-PH in rats.

Genome-wide association studies have identified two independent genetic variants upstream of the SRY-box transcription factor 17 (Sox17) gene promoter that are associated with PAH. However, mechanisms by which Sox17 mutations lead to PAH are not understood. Notably, RUNX1 is an important downstream target of SOX17. We hypothesized that impaired Sox17 expression predisposes to PAH by failing to suppress RUNX1.

Mice with deletion of the Sox17 signal 1 enhancer region (Sox17eKO) were generated to resemble the mutations in PAH patients (from Dr. Lan Zhao, Imperial College London, UK). Low dose (5 mg/kg) Sugen 5416 and mild hypoxia (12% O2) induced PH in Sox17eKO mice but not in wild-type mice, suggesting that Sox17eKO mice are more susceptible to developing SuHx-PH. Sox17 and Runx1 gene expression in bone marrow from Sox17eKO and WT mice were inversely related at baseline and during SuHx- PH. The specific RUNX1 inhibitor Ro5-3335 reversed SuHx-PH in Sox17eKO mice. Next, we generated triple transgenic mice, and found that inducible endothelial deletion of Runx1 in adult Sox17eKO mice abrogates susceptibility to SuHx-PH. These results support the hypothesis that PH associated with impaired Sox17 expression is mediated in part by RUNX1 and that RUNX1 may represent a novel target for treating PAH.

HIPK2 is a potential target for smooth muscle focused anti-remodeling therapy in pulmonary arterial hypertension.

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Pulmonary arterial hypertension (PAH) is a progressive deadly disease with no cure. Increased proliferation and survival of pulmonary arterial smooth muscle cells (PASMC), coupled with metabolic reprograming are key components of pulmonary vascular remodeling in PAH. We recently demonstrated that transcriptional coregulator homeodomain-interacting protein kinase-2 (HIPK2) supports pro-proliferative/pro-survival phenotype of PAH PASMC, however the mechanisms of this regulation are understudied.

We found that HIPK2 is upregulated in smooth muscle alpha actin-positive areas of small remodeled PAs and primary PASMC from PAH patients compared to non-diseased subjects. Pharmacological inhibition of HIPK2 (tBID) in human PAH PASMC significantly decreased growth, proliferation, induced apoptosis, and significantly decreased levels of pro-proliferative/pro-survival transcriptional co-activator YAP/TAZ and regulator of cytokinesis CEP55. We found the over-accumulation of YAP and CEP55 in human PAH PASMC, and its depletion reduced cell proliferation, and induced apoptosis, suggesting that HIPK2 promotes increased proliferation and survival of PAH PASMC through YAP and CEP55. Interestingly, inhibition of HIPK2 or depletion of CEP55 down-regulated elevated key lipid metabolism enzymes ACLY and ACC in human PAH PASMC, suggesting that HIPK2 could coordinate cell metabolism in PAH PASMC. Importantly, HIPK2 downregulation by tBID significantly decreased overproduction of extracellular proteins Fibronectin and Collagen 1A in PAH PASMC. Most importantly, in vivo HIPK2 inhibitor attenuated SU5416/Hypoxia-induced PH in mice as evidenced by significant decrease of systolic right ventricular pressure compared to the vehicle-treated group. Overall, even further studies are needed, the HIPK2 can be considered as potential target for developing novel anti-remodeling therapy for PAH.
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Alternative Polyadenylation Drives Vascular Remodeling in Pulmonary Hypertension.

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Introduction: Pulmonary Arterial Hypertension (PAH) is a disease characterized by pulmonary vascular remodeling and increased pulmonary artery pressures. This remodeling is driven by a phenotypic change in Pulmonary Artery Smooth Muscle Cells (PASMCs) from a contractile to a synthetic phenotype. One mechanism that drives changes in PASMCs is alternative polyadenylation (APA). APA happens when there is a shift in the polyadenylation (polyA) site used during mRNA maturation resulting in transcripts with varying 3'UTR lengths. One driver of APA in PASMC is reduced expression of NUDT21, which contributes to global 3' UTR shortening and transcriptional dysregulation.

Methods: Research was conducted with patient samples and the hypoxia mouse model of PH. The human lung samples are from patients with PAH and matched donors. Protein expression was assessed by western blot and immunohistochemistry. RNA levels and polyadenylation site changes where measured by RNA- seq and confirmed by qRT-PCR.

Results: NUDT21 is reduced in the hypoxia mouse model leading to increased vascular pressures. Additionally, depletion of NUDT21 in this model results in exacerbated PH seen even in normoxic conditions. Cell culture experiments define a role of NUDT21 depletion in increased proliferation and migratory changes in isolated patient PASMCs. Further analysis revealed 3'UTR shortening of core-factor binding beta (CBFB), prostaglandin EP3 receptor (PTGER3) and hyaluronan synthase 2 (HAS2) as targets of APA, regulated by NUDT21.

Conclusions: NUDT21 depletion promotes vascular remodeling and features of PH as well as PASMC phenotype changes. Understanding the network of transcripts regulated by APA is key to designing interventions that are able to target vascular remodeling in PAH, which remains as an important barrier to treat established disease.

Epigenetic regulation of endothelial Anoctamin1 in pulmonary arterial hypertension.

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Introduction/Hypothesis: Hyperproliferative and apoptosis resistant pulmonary artery endothelial cells ECs play a critical role in pulmonary arterial hypertension (PAH), leading to occlusive plexiform lesions, and increased pulmonary vascular resistance. ECs isolated from patients with idiopathic PAH had increased proliferation compared to ECs from control patients. We previously reported that Anoctamin-1 (ANO1), a calcium-activated chloride channel, expression is increased in lung ECs from patients with PAH and is associated with

increased EC proliferation. Furthermore, we found that overexpression of wild-type ANO1 in human pulmonary artery ECs leads to apoptosis resistance, decreased mitochondrial (mito) respiration, and depolarized mito membrane potential compared to control cells. However, the regulatory mechanism underlying ANO1 expression in PAH remains unclear. DNA methylation has been recognized as an important mechanism regulating gene expression. In this study, we test the hypothesis that ANO1 expression in PAH is epigenetically regulated via DNA methylation.

Methods/Results: DNA was extracted from lung ECs of patients with idiopathic PAH (n=7) and controls (n=6), followed by Bisulfite Next-Generation Sequencing (EpigenDx, MA) to determine DNA methylation profile in human ANO1 gene (Ensembl Gene ID: ENSG00000131620). We used 19 assays to cover 97 CpG sites in the human ANO1 gene, including regions of 5'-upstream, 5'-UTR, and different introns. Our data show that the methylation of 29 of 97 (30%) CpG sites in human ANO1 gene is significantly altered in lung ECs from PAH patients than that from control subjects. Among the significantly altered 29 CpG sites, the methylation at 22 CpG sites (76%) is significantly decreased. We developed a CRISPR-based approach to target four differentially methylated CpG sites to determine the specific contribution of their methylation in regulation of human ANO1 gene. We demonstrate that demethylation of one of the sites, CpG#-73, in human embryonic kidney cells resulted in an increase in ANO1 mRNA expression compared to control, suggesting that decreased DNA methylation is sufficient to upregulate human ANO1 expression. Conclusions: Our results demonstrate that DNA methylation in human ANO1 gene is significantly altered in PAH and reduction in DNA methylation may serve as a regulatory mechanism for ANO1 upregulation in settings of PAH.

Single Nuclear RNA Sequencing of Liver from Patients with Portopulmonary Hypertension as a Tool for Biomarker Discovery.

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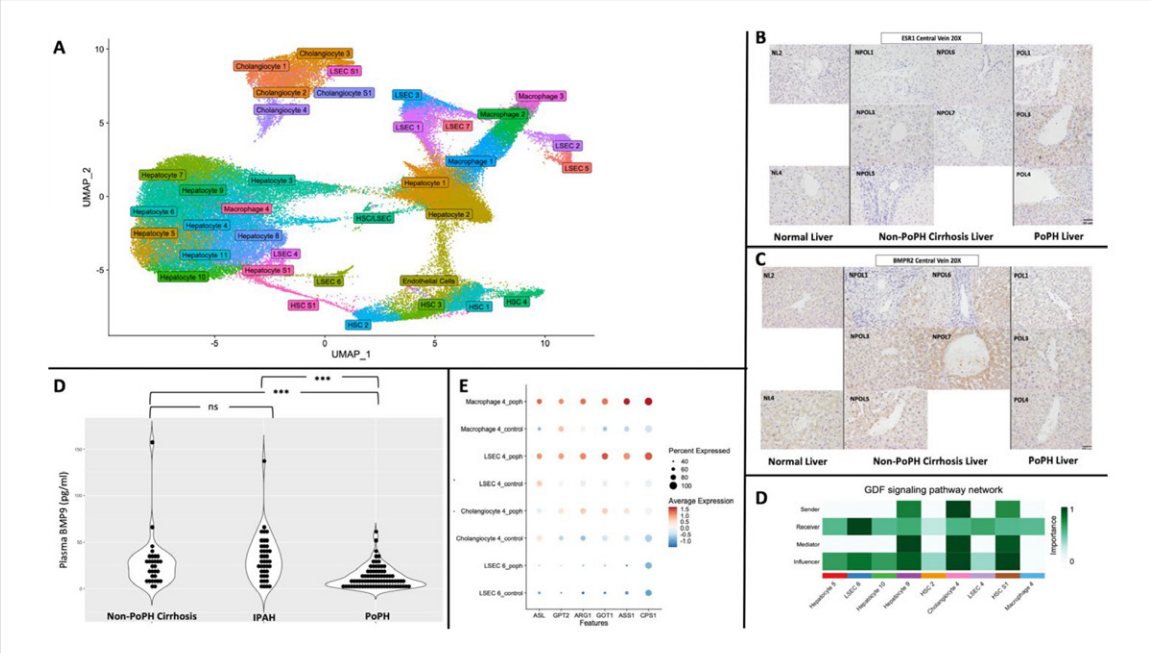
Portopulmonary hypertension (PoPH) is a type of pulmonary arterial hypertension (PAH) due to portal hypertension with high mortality. The mechanisms driving disease pathogenesis are unknown, and transcriptional characteristics unique to the PoPH liver remain unexplored. Addressing this gap, we applied single nuclear RNA sequencing to compare liver tissue from patients with PoPH to those with non-PoPH cirrhosis.

Analyzing transcriptomic data (Fig 1-A), unique characteristics of the region surrounding the hepatic central vein were observed, including decreased expression of the bone morphogenic protein type II receptor (BMPR2) and increased estrogen receptor type I (ESR1) genes (validated using immunohistochemistry, Fig 1-B and 1-C), and enriched

growth differentiation factor (GDF, Fig 1-D) and arginine biosynthesis (Fig 1-E) signaling. Although differential expression of the bone morphogenic protein type 9 (BMP9) gene was not observed, we confirmed significantly lower levels of plasma BMP9 in PoPH relative to non-PoPH cirrhosis and idiopathic PAH (Fig 1-D). These results provide insight into the transcriptomic characteristics of the PoPH liver, suggest potential mechanisms by which PoPH central venous cellular dysfunction contributes to pulmonary vascular remodeling along several pathways (GDF signaling, arginine biosynthesis, BMP9, BMPR2, and ESR1 signaling), and demonstrate how integration of transcriptomics with proteomic and metabolomic approaches can inform biomarker discovery and clarify mechanisms of PAH disease pathogenesis.



Novel Mechanism of PDH Deficiency in PAH: A Precision Medicine Path Toward Overcoming Therapy Resistance.

Maki Niihori, Joel James, Ruslan Rafikov, Olga Rafikova.

Department of Medicine, Indiana University

Pulmonary arterial hypertension (PAH) is a progressive fatal disease associated with severe metabolic disturbances. The insufficiency of pyruvate dehydrogenase (PDH), one of the critical metabolic regulators, was directly implicated in the pathogenesis of PAH. The mechanism of PDH inhibition involves the overactivation of PDH inhibitor pyruvate dehydrogenase kinase (PDK). However, therapeutic efforts focusing on PDK have shown that only a subset of PAH patients respond to PDK inhibition. These results imply the unknown PDK-independent mechanisms of PDH deficiency, underscoring the need for better patient stratification.

We discovered that idiopathic PAH (iPAH) patients show a reduced binding between PDH and its critical co-factor, lipoic acid (LA). The activity of the LA-producing enzyme, LA synthase, depends on the adequate work of the FeS cluster scaffold protein NFU1. Given the high prevalence of PAH among NFU1 mutation carriers, we engineered a novel rat model mimicking the human NFU1 mutation. NFU1^{G206C} rats spontaneously developed a severe mitochondrial dysfunction and progressive PAH phenotype characterized by an ongoing loss of small pulmonary artery's density, severe vaso-obliterative disease, endothelial barrier disruption, impaired right ventricle (RV) metabolism, and RV dysfunction.

Supplementation of LA in drinking water restored PDH activity and mitochondrial function and rescued the PAH phenotype in NFU1^{G206C} rats. This protection was sufficient to preserve pulmonary angiogenesis and barrier function and prevent vascular and RV remodeling.

Our study emphasizes the consequential role of PDH dysfunction, induced by LA deficiency, in PAH's multifaceted pathology. The impaired NFU1 expression and PDH lipoylation in the lungs of iPAH patients suggest that the PDH deficiency in these patients would be resistant to PDK inhibitors but potentially correctable by LA supplementation.

Hypusine Signaling: A Novel Pathway Driving Vascular Remodeling in Pulmonary Arterial Hypertension.

Sarah-Eve Lemay[1], Yann Grobs[1], Sandra Martineau[1], Mabrouka Salem[1], Tsukasa Shimauchi[1], Sandra Breuils-Bonnet[1], Alice Bourgeois[1], Charlie Théberge[1], François Potus[1], Steeve Provencher[1], Sébastien Bonnet[1], Olivier Boucherat[1].

[1]*Pulmonary Hypertension research group, CRIUCPQ-UL, Quebec, Canada*

Pulmonary Arterial Hypertension (PAH) is characterized by progressive distal pulmonary arteries (PAs) obstruction leading to heart failure and death. PA smooth muscle cells (PASMCs) from PAH patients display a "cancer-like" phenotype that contributes to PA remodeling. Eukaryotic translation initiation factor 5A (eIF5A) provides cancer cells with a competitive advantage by increasing translation of mRNAs with oncogenic proprieties. Strikingly, eIF5A is the sole protein containing the unique spermidine-derived amino acid hypusine required for its function. Hypusine formation is catalyzed by the sequential actions of Deoxyhypusine synthase (DHPS) and Deoxyhypusine hydroxylase (DOHH). We hypothesized that hypusine signaling is increased in PAH and contributes to pulmonary vascular remodeling.

As assessed by LC-MSMS and WB, expression levels of DHPS, DOHH and both total and hypusinated forms of eIF5A were found increased in PAs and PASMCs from PAH patients and animal models. In vitro, both molecular and pharmacological inhibition of DHPS and DOHH significantly attenuated PAH-PASMCs survival (WB Survivin; Annexin V labeling) and proliferation (WB MCM2, PLK1; Ki67 labeling and EdU incorporation). Hypusine signaling promoted the expression of a broad array of proteins involved in oxidative phosphorylation, supporting the bioenergetic requirements of cell survival and proliferation (LC-MSMS, WB, Seahorse). In vivo, smooth muscle cells-targeted inactivation of one allele of Dhps conferred

partial protection against the development of Sugen/Hypoxia (Su/Hx)-induced PAH in mice. Accordingly, pharmacological inhibition of DHPS using GC7 improved hemodynamics (RVSP, mPAP, CO) and vascular remodeling (EVG) in monocrotaline and Su/Hx rats with established PAH.

In conclusion, Hypusine signaling is implicated in PAH development and represents a new promising target.

Lipidomic associations with pulmonary vascular-right ventricular function: a lipidome-wide Association study.

Catherine Simpson[1], Ethan Gough[1], Karthik Suresh[1], Steven Hsu[1], Rachel Damico[1], and Paul Hassoun[1].

[1]*Johns Hopkins University*

Background: We and others have demonstrated aberrant lipid metabolism in pulmonary vascular (PV) diseases. Decreased fatty acid oxidation and intracellular lipid accumulation are broadly implicated in right ventricular (RV) failure in pulmonary hypertension, however no prior studies have granularly assessed dysregulated lipid metabolism, using high-resolution lipidomic data, in relation to comprehensively measured RV-PV function. We hypothesized that distinct lipidomic signatures would relate to RV-PV function.

Methods: We performed multi-beat rest/exercise right heart catheterization and RV pressure-volume loop analysis in 89 subjects. Mass spectrometry-based lipidomic profiling was performed on blood collected intra-procedurally using Metabolon's complex lipid platform. Lipidomic associations with hemodynamics and comprehensive measures of RV function were determined via regression modeling, fold-change analyses, and enrichment analyses overlaid onto lipid pathway networks in R v4.2.3.

Results: Of 1,207 lipid molecules quantitated, 13.4% associated with three or more resting ventriculo- arterial parameters. Circulating long-chain lactosylceramide and lysophosphatidylcholine species associated with lower pulmonary pressures and favorable RV function. Across classes, lipid species with fatty acid (FA) 16:1 (palmiteolate) residues associated with higher pulmonary pressures and worse RV contractility and RV-PA coupling, while species with FA20:4 (arachidonic acid) residues were associated with better global RV function. Phospholipid species with FA22:0, FA20:2, and FA22:5 residues were strongly associated with poor contractility. Similar overall patterns were seen in association with exercise parameters; FA20:4 residues predicted favorable RV exercise performance (not shown).

Enrichment analysis implicated dysregulated metabolism of glycerolipids (chiefly triacylglyerols), arachidonic acid and its precursor, linoleic acid, and other sphingolipid and phospholipid species in distinguishing coupled versus decoupled RV-PV units.

Conclusions: Distinct lipid profiles correspond to specific gold-standard RV-PV measurements. Lipidomic profiling may illuminate novel diagnostic markers and therapeutic targets.

Figures.

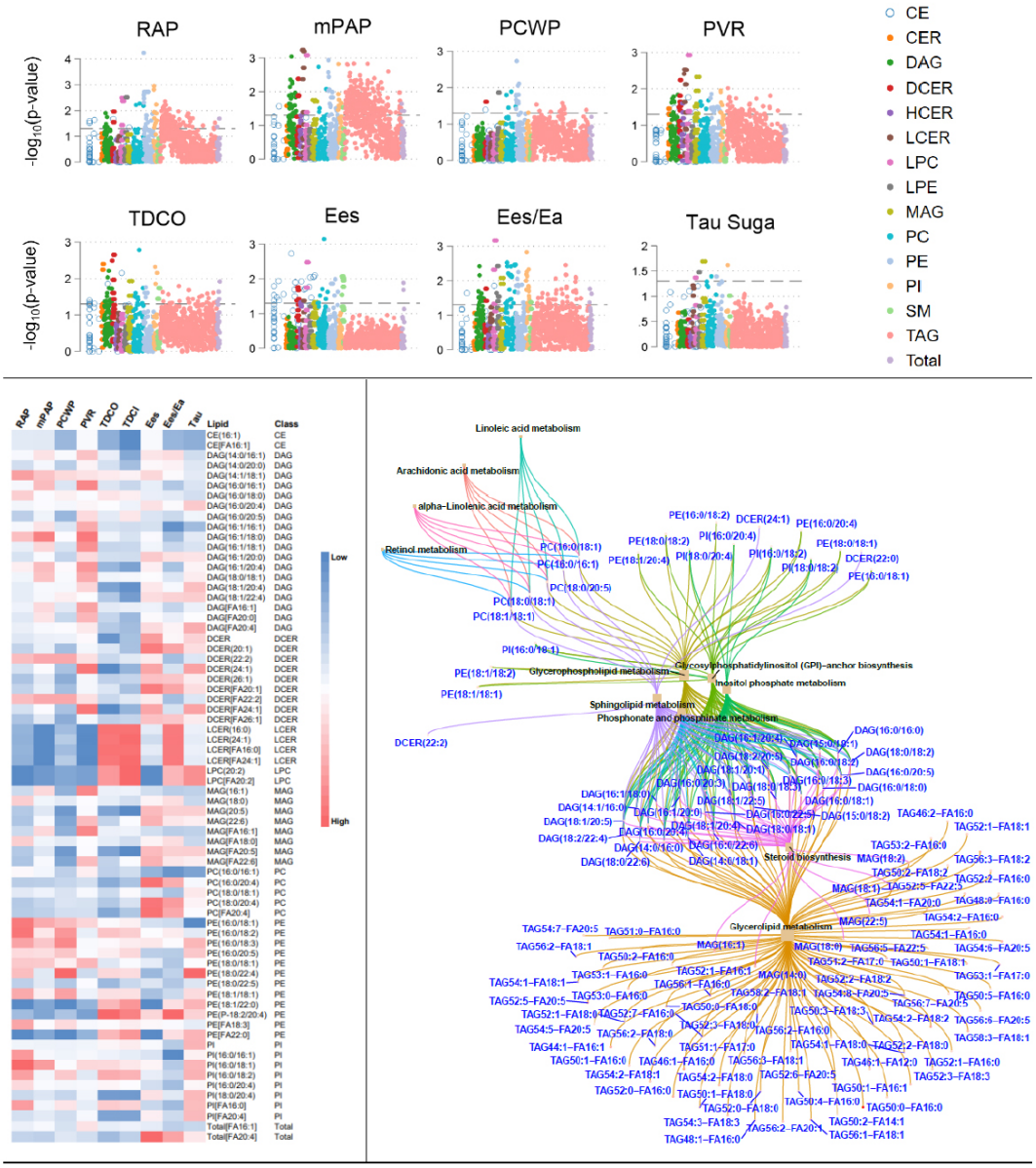


Figure. Manhattan plots depict unique lipidomic signatures for resting ventriculo-arterial parameters (upper panel); summary heat map of lipid-phenotype associations for lipids (excluding TAGs) with >=3 significant associations with resting ventriculoarterial parameters (left lower panel); lipid pathway network with overlaid enrichment analysis depicting lipids with significant fold-change in subjects with coupled versus de-coupled RV-PV units (Ees/Ea thresholded at 1.0) generated via *MetENP* for R version 4.2.3 (right lower panel). Individual lipids are labeled with blue text, and pathways are labeled with black text. Individual lipid nodes are represented by circles, and lipid pathway nodes are represented by squares. Square size corresponds to the number of associated branches. All data presented is limited to rest data; exercise data not shown. *Abbreviations*: RAP: right atrial pressure; mPAP: mean pulmonary arterial pressure; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; TDCO: thermodilution cardiac output; Ees: end-systolic elastance (e.g., contractility); Ees/Ea: ratio of Ees to arterial elastance (e.g., ventriculoarterial coupling; CE: cholesteryl ester; CER: ceramide; FA: fatty acid; DAG: diacylglycerol; DCER: dihydroceramide; HCER: hexosylceramide; LCER: lactosylceramide; LPC: lysophosphatidylcholine; LPE: lysophosphatidylethanolamine; MAG: monoacylglycerol; PC: phosphatidylcholine; PE: phosphatidylethanolamine; PI: phosphatidylinositol; SM: sphingomyelin; TAG: triacylglycerol.

LDHA-lactate-dependent lactylation of TOP1 and EMILIN1 promotes pulmonary vascular cell proliferation and pulm.

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Pulmonary arterial hypertension (PAH) is a progressive disease characterized by remodeling of small pulmonary arteries (PAs) due to hyper-proliferation of resident PA cells. Metabolic shift to glycolysis of PAH PA smooth muscle (SM) cells (PASMC) results in the lactate over-production, the role of which in PAH is unknown. We found that lactate dehydrogenase A (LDHA) was over- expressed in SMα-actin-positive areas of small muscular PAs in human PAH and rodent SuHx PH, and distal human PAH PASMC, promoting lactate-dependent hyper-proliferation. Lysine lactylation (Kla) was selectively increased in human PAH PASMC *in vivo* and *in vitro*. Proteomic analysis identified 12 hyper-lactylated non-histone proteins in PAH PASMC vs. controls. Further validation revealed that hyper-lactylation induced PASMC-specific over-accumulation of TOP1 and deficiency of EMILIN1 in PAH lungs, leading to up-regulation of Yap/Taz, Akt-mTOR, TGFβ1, and hyper-proliferation. Human PAH PASMC had elevated lactate secretion; exogenous lactate induced proliferation of PAEC and PAAF. *SM22α-Ldha-/-* mice were protected from SuHx- induced PA remodeling, PH, and RV hypertrophy. LDHA inhibitor oxamate reduced proliferation and promoted apoptosis in human PAH PASMC, reversed SuHx-induced TOP1 and Akt up- regulation, PA remodeling, PH, and RV hypertrophy in mice. Collectively, our data demonstrate that LDHA-driven lactate over-production promotes proliferative, apoptosis-resistant PASMC phenotype, PA remodeling, and PH via hyper-lactylation and over-accumulation of TOP1, deficiency of EMILIN1, and consequent activation of Yap/Taz, Akt/mTOR, and TG geting LDHA-lactate network could represent potentially attractive strategy to treat PAH.

ATP Citrate Lyase (ACLY): a Promising Target Against Vascular Remodeling Development.

Yann Grobs[1], Charlotte Romanet[1], Sarah-Eve Lemay[1vv], Alice Bourgeois[1v], Sandra Breuils Bonnet[1v]; Reem El-Kabbout[1], Charlie Theberge[1], Sandra Martineau[1], Pierre Voisine[1,2], François Potus[1,2], Steeve Provencher[1,2], Olivier Boucherat[1,2], Sébastien Bonnet[1,2].

[1]Laval University, Quebec, QC, Canada, [2]IUCPQ research center, Quebec, QC Canada

Pulmonary arterial hypertension (PAH) is a progressive vascular remodeling (VR) disease (VRD) in which pulmonary artery (PA) smooth muscle cells (PASMC) are characterized by excessive proliferation and resistance to apoptosis, like in cancer cells. These features are shared with neointimal hyperplasia (NH) in coronary artery disease (CAD). VR in both PAs and CAs lead to heart failure. ATP citrate lyase (ACLY), an enzyme has recently emerged in cancer as a key player to sustain VRD-SMCs abnormal phenotype by favoring Warburg

effect, chromatin remodeling by acetylation, and lipid synthesis, making an attractive target. However, its role in VRD remains unknown. Thus, we hypothesized that ACLY is upregulated in VRD and supports the abnormal phenotype of VRD-SMCs. Increased expression and nuclear localization of ACLY were observed in PA, PASMCs from PAH and in CoA and CoASMCs of CAD patients compared to controls (immunoblot, IB/immunofluorescence, IF) as well as in PAH&CAD animal models (SugenHypoxia, SuHx&carotid injury, CI). ACLY inhibition impedes VRD-SMC bioenergetics and lipid metabolism (OCR/ECAR ratio, RNASeq) and decreased histones acetylation leading to reduced SMC proliferation and survival (Ki67&AnnexinV, IF, PCNA&Survivin, IB). In vivo, pharmacological inhibition of ACLY in SuHx rat model significantly improved pulmonary hemodynamics (mPAP) and RV function (CO). Consistency, PAs remodeling was reduced by ACLY inhibition. In agreement with this, we found that inactivation of Acly targeted to SMCs confers protection against SuHx-induced PAH and CI-induced NH in mice. In onstrated that inhibition of ACLY may represent a novel and attractive therapeutic avenue to correct VRD.

Distinct Proteomic Signatures are Associated with Right Ventricular Outcomes in Pulmonary Arterial Hypertension.

Hongyang Pi, MD MS[1,2]; Lu Xia, PhD[3]; Samuel G Rayner, MD[1]; Ali Shojaie, PhD[2]; Sina A. Gharib, MD[1]; Peter J. Leary, MD PhD[1,4].

[1]University of Washington, Department of Medicine; [2]University of Washington, Department of Biostatistics; [3]Michigan State University, Department of Statistics; [4]University of Washington, Department of Epidemiology

Rationale: Pulmonary arterial hypertension (PAH) is a complex disease characterized by progressive right ventricular (RV) failure leading to significant morbidity and mortality. Investigating proteomic features and pathways associated with mortality and RV dilation can provide insight into molecular mechanisms, define phenotypes in RV adaptation, and identify potential therapeutic targets.

Methods: The Seattle Right Ventricle Translational Science Study (Servetus) is a single institution cohort enrolled between 2014 and 2016 and followed for three years. All participants underwent untargeted proteomic profiling on 7288 aptamers (targeting 6467 unique human proteins) from circulating blood using SomaScan. Partial least squares discriminant analysis (PLS-DA) was applied to assess the distinguishability of relevant outcomes including mortality, RV dilation, and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels. Differentially abundant proteins were then identified using Cox regression, and linear regression models (as appropriate for the specific outcome) with adjustments for age, sex, body mass index and PAH etiology. Pathway enrichment analysis was performed to identify significantly dysregulated processes in outcomes. Models exploring RV maladaptation were further adjusted for pulmonary vascular resistance (PVR).

Results: A total of 117 participants with World Health Organization Group 1 PAH were included. PLS-DA showed clear separations between survivors and non-survivors, participants with dilated versus non-dilated RVs, and across a range of NT-proBNP levels. Proteins and pathways involving the extracellular matrix (ECM) were upregulated in

participants who died during follow-up, those with severe RV dilation, and higher levels of NT-proBNP. The ECM signal was further strengthened when PVR was adjusted in all models. Moreover, proteins and pathways related to the immune system were downregulated in those who died but not present in the PVR- adjusted survival analysis.

Conclusions: Distinctive plasma proteomic profiles are associated with mortality, RV dilation, and NT-proBNP in PAH. ECM remodeling pathways represent promising candidates for identifying patients at high risk for poor outcomes and for investigation into their roles as markers or mediators of RV vulnerability.

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