The Pulmonary Fibrosis Foundation presents

IPF SUMMIT 2011
FROM BENCH TO BEDSIDE

DECEMBER 1, 2011
5:00 PM–7:30 PM

DECEMBER 2, 2011
7:00 AM–5:45 PM

DECEMBER 3, 2011
7:00 AM–3:45 PM

Marriott Magnificent Mile
Chicago, Illinois

Physicians, Researchers, Registered Nurses, and Allied Health Professionals
Dear Friends of the Foundation,

Welcome to the IPF Summit 2011: From Bench to Bedside. This is our inaugural scientific healthcare conference where we are bringing together some of the best and the brightest in the PF community. It is our hope that fostering this type of collaboration will lead to improved diagnosis, better patient care, and help stimulate the research needed to find better treatments and ultimately a cure for IPF. We are pleased to be able to provide sessions for both the professional and patient/caregiver populations. Patient support and education is an important component of our mission, and in order to supply as many patients, caregivers, and family members with this information, we are providing a live webcast for the patient/caregiver sessions.

As many of you know, I have a personal connection to IPF. The Foundation was the brainchild of my father Albert Rose and his brother Mike Rosenzweig, who had been both recently diagnosed with IPF when the Foundation was started. Their sister Claire had died from pulmonary fibrosis a few years earlier, and they both felt a profound need to help find a cure for this devastating disease. My father died in early 2002, but his brother continued to work unstintingly and passionately to build the Foundation, fund research, and create a financially viable entity. Over the past decade the Foundation has also significantly expanded its support network and has become a beacon for those afflicted with this deadly disease. I am extremely honored to carry on their legacy as President and Chief Executive Officer for the Foundation.

This Summit is a milestone for the Foundation as we celebrate our tenth anniversary. Many people have worked hard for the past two years to make the Summit come to fruition. I would like to thank the Foundation’s staff and our partners, The France Foundation and National Jewish Health, for what was truly a team effort in making this event a success. Of course, many thanks must go to our “all star” Faculty for sharing with us their knowledge and expertise. Lastly, I would like to thank our generous sponsors, both individual and corporate, for their generosity.

I have been doing quite a bit of traveling during the last few months attending some medical conferences, participating in fundraising events, and engaging in advocacy activities for the Research Enhancement Act. A couple of things have greatly impressed me. First, there is considerable interest in drug development for IPF. The research community is working hard to discover new and successful agents. There are a number of exciting therapies that are in early development while others are working their way through the clinical trial process. Parenthetically, it is critically important for the patient community to participate in clinical trials. This is the only way we can develop new, effective treatments. Lastly, I am continually impressed and motivated by the courage and commitment of the patients and their family members. They are a constant source of inspiration for all of us that are associated with the Foundation, and I assure everyone that we will work tirelessly and passionately to help find a cure for this illness!

Warmest Regards,

Daniel M. Rose, MD
President and Chief Executive Officer
Dear Colleagues,

It is a true pleasure to welcome you to the *IPF Summit 2011: From Bench to Bedside*. Despite two decades of progress, our understanding of the pathobiology and more importantly our ability to treat idiopathic pulmonary fibrosis (IPF) remains woefully inadequate. Because of this, we felt it important to have a focused, innovative conference to help expand our knowledge and to encourage the development of new treatment options. It is obvious that no one person can answer the big questions in IPF, that is why so many physicians, researchers, patients, family members, and industry representatives are here today; to learn, to collaborate, and to share information.

The *IPF Summit* has been organized by the Pulmonary Fibrosis Foundation in order to provide the most up-to-date material to the medical and research communities, as well as to be a source of information and support for those affected by this disease. This international conference includes a faculty of distinguished experts in the field of pulmonary fibrosis who have put together an outstanding program. While we will not answer all of the questions, here is an opportunity to bring talented and dedicated people together to work towards a single goal: making a difference to those who suffer from IPF.

I am honored and excited to be the Program Chair for the *IPF Summit 2011*, and thank each of you for your attendance and for your willingness to share your experience, knowledge, and expertise. Your engagement and input throughout the *Summit* will help shape the next decade of pulmonary fibrosis research, and with our collective efforts we can improve the future of those affected by this terrible disease.

Sincerely,

Kevin K. Brown, MD
Professor and Vice Chair, Department of Medicine
National Jewish Health

Pulmonary Fibrosis Foundation’s Medical Advisory Board, Chair
*IPF Summit 2011: From Bench to Bedside*, Program Chair
# Table of Contents

About the Pulmonary Fibrosis Foundation..............................................................................................................................................................1
PFF Research Fund to Cure Pulmonary Fibrosis ..................................................................................................................................................6
Meeting Information and Procedures.................................................................................................................................................................7
IPF Summit 2013 …......................................................................................................................................................................................................9
New Decade, New Reach Tenth Anniversary Dinner .................................................................................................................................10
Agenda ...........................................................................................................................................................................................................11
Navigating the Summit: Meeting Space Map ..............................................................................................................................................15
Activity Information ......................................................................................................................................................................................................18
Learning Objectives ......................................................................................................................................................................................................18
Accreditation Statements ..................................................................................................................................................................................................18
Program Faculty ......................................................................................................................................................................................................19
Faculty Disclosures ......................................................................................................................................................................................................22
Attendee List ........................................................................................................................................................................................................25
Pulmonary Fibrosis Foundation Sponsors .....................................................................................................................................................29
Exhibitors ........................................................................................................................................................................................................30
Posters ........................................................................................................................................................................................................33
Academic Posters ......................................................................................................................................................................................................33
Industry Posters ......................................................................................................................................................................................................68
Friday Sessions ......................................................................................................................................................................................................77
Lung Injury and Repair ...................................................................................................................................................................................................77
Genetics and Biomarkers ................................................................................................................................................................................................83
Drug Development in IPF ................................................................................................................................................................................................89
Saturday Sessions ......................................................................................................................................................................................................95
Clinical Sessions .......................................................................................................................................................................................................95
Update on Transplantation ................................................................................................................................................................................................101
About the Pulmonary Fibrosis Foundation

Mission
The mission of the Pulmonary Fibrosis Foundation (PFF) is to help find a cure for idiopathic pulmonary fibrosis (IPF); advocate for the pulmonary fibrosis community both locally and in Washington, DC; promote disease awareness; and provide a compassionate environment for patients and their families.

History
The Pulmonary Fibrosis Foundation is a 501(c)(3) nonprofit organization that was founded in 2000 by two brothers, Albert Rose and Michael Rosenzweig, PhD. Their sister Claire had died from idiopathic pulmonary fibrosis (IPF), and the brothers were both later diagnosed with the disease. Their vision shaped the PFF to become a leader in the IPF community for research, advocacy, awareness, and support. In February of 2002, sad to say, Albert Rose succumbed to the disease.

Dr. Rosenzweig was the Foundation’s first President and Chief Executive Officer. He worked tirelessly and passionately to build the Foundation, fund research, and create a financially viable entity. He also helped recruit an outstanding Medical Advisory Board, which has provided keen insight and direction.

Unfortunately, due to the progression of his disease, Dr. Rosenzweig retired as President and CEO in March 2009. Daniel M. Rose, MD, the son of Albert Rose and chairman of the Board of Directors, then assumed the positions of President and CEO. Dr. Rose had previously been a practicing cardiothoracic surgeon and Chief of Cardiothoracic Surgery at St. Vincent’s Medical Center in Bridgeport, Connecticut, for 19 years. Having had three relatives afflicted with IPF, he brings to the Foundation a family member’s passion and motivation, along with a broad medical background and a profound desire to lead the PFF into its second decade.

Under Dr. Rose’s guidance the PFF has embarked on several ambitious initiatives to:

• Increase funding for IPF research and assist in creating partnerships between the academic research community and the biopharma industry.
• Foster the sharing of information and ideas in the clinical community through the creation of a biennial IPF Summit, beginning in 2011.
• Help create a national pulmonary fibrosis registry.
• Sponsor a series of webinars to more efficiently bring the latest information and research to patients and families.
• Establish a National Affiliate Program, which will increase patient outreach, enhance advocacy, expand disease awareness, and augment our fundraising.
• Continue our commitment to strongly advocate for the IPF community locally and in Washington, DC.
• Aggressively pursue increased public awareness through a series of public service announcements (PSA), social networking, and traditional media exposure.

www.ipfsummit.org
Board of Directors

Daniel M. Rose, MD*
President and Chief Executive Officer

Joseph Borus, Esq*
Secretary

Thomas E. Hales*
Treasurer

Patti Tuomey, EdD
Chief Operating Officer

*Denotes Executive Committee

Pulmonary Fibrosis Foundation Team

Daniel M. Rose, MD
President and Chief Executive Officer

Patti Tuomey, EdD
Chief Operating Officer

Dolly Kervitsky, CRT, CCRC
Vice President
Patient Relations

Scott Staszak
Associate Vice President
Finance and Information Technology

Cara Schilling
Associate Vice President
Communications and Marketing

Jennifer Bulandr

Amy Butler

Lyla Conrad

Peter Cremer

Matt Derda

Wendy Escobar

Courtney Firak

Mary Lou Ibadlit

Meredith Mann

Jennifer Mefford

Amanda Miller

Michelle Miller

Susan Murphy

Elizabeth Price

Francisco Rosas

Stephanie Seweryn

Leanne Storch

www.pulmonaryfibrosis.org
Medical Advisory Board

*Indicates Member of the Research Advisory Committee

Kevin K. Brown, MD*
CHAIRMAN
Vice Chair, Department of Medicine
Professor of Medicine
National Jewish Health
Denver, Colorado

David W. Kamp, MD
MEDICAL DIRECTOR
Professor of Medicine
Associate Chief, Pulmonary and Critical Care Division
Northwestern University Medical School
Chief, Pulmonary
Jesse Brown VA - Northwestern University Affiliate
Chicago, Illinois

Jesse Roman, MD*
CHAIRMAN, RESEARCH ADVISORY COMMITTEE
Professor of Medicine
Chairman, Department of Medicine
Pulmonary, Critical Care, and Sleep Disorders Medicine
University of Louisville
Louisville, Kentucky

Marvin I. Schwarz, MD
PAST-CHAIRMAN
Professor of Medicine Division Co-Head
University of Colorado
Denver, Colorado

Timothy S. Blackwell, MD*
Professor of Medicine
Professor of Cancer Biology
Ralph and Lulu Owen Chair in Medicine
Professor of Cell and Developmental Biology
Vanderbilt University Medical Center
Nashville, Tennessee

Jeffrey T. Chapman, MD
Chair, Quality and Patient Safety
Cleveland Clinic Abu Dhabi
Abu Dhabi, United Arab Emirates

Harold R. Collard, MD
Associate Professor of Medicine
Director, Interstitial Lung Disease Program
Division of Pulmonary and Critical Care Medicine
University of California, San Francisco
San Francisco, California

Rany Condos, MD
Associate Professor of Medicine
School of Medicine at New Bellevue Chest Group
New York University
New York City, New York

Gregory P. Cosgrove, MD
Associate Professor of Medicine
Department of Medicine
Co-Director, Interstitial and Autoimmune Lung Disease Program
National Jewish Health
University of Colorado
Denver, Colorado

Roland M. duBois, MD
Emeritus Professor of Respiratory Medicine
National Heart and Lung Institute
Imperial College
University of London
London, United Kingdom

Christine Kim Garcia, MD, PhD
Associate Professor of Medicine
McDermott Center for Human Genetics
Department of Internal Medicine, Division of Pulmonary and Critical Care Medicine
University of Texas Southwestern Medical Center
Dallas, Texas

Susan S. Jacobs, RN, MS
Center for Interstitial Lung Disease
Pulmonary and Critical Care Medicine
Stanford University Medical Center
Stanford, California

Naftali Kaminski, MD*
Professor of Medicine, Pathology, Human Genetics and Computational Biology
Director, Dorothy P. and Richard P. Simmons Center for Interstitial Lung Disease
Director, Lung, Blood and Vascular Center for Genomic Medicine
Pittsburgh, Pennsylvania

www.ipfsummit.org
Joseph Lasky, MD*
Professor of Medicine
Section of Pulmonary Diseases
Co-Director, Interstitial Lung Disease Clinic
TCC Program Member
Tulane University
New Orleans, Louisiana

Andrew H. Limper, MD*
Professor of Medicine
Chair, Pulmonary and Critical Care Medicine
Mayo Clinic
Rochester, Minnesota

Kathleen Lindell, PhD, RN
Clinical Nurse Specialist
Director, Quality of Life Program
Division of Pulmonary, Allergy, and Critical Care Medicine
Dorothy P. and Richard P. Simmons Center for Interstitial Lung Disease
University of Pittsburgh
Pittsburgh, Pennsylvania

James E. Loyd, MD*
Professor of Medicine
Director, Familial Primary Pulmonary Arterial Hypertension Registry
Director, Familial Idiopathic Pulmonary Fibrosis Registry
Vanderbilt University Medical Center
Nashville, Tennessee

David Lynch, MD
Professor of Radiology
Co-Director, Division of Radiology
National Jewish Health
Denver, Colorado

Fernando J. Martinez, MD, MS*
Professor, Department of Internal Medicine
Director, Pulmonary Diagnostic Services
University of Michigan
Ann Arbor, Michigan

Imre Noth, MD
Associate Professor of Medicine
Director, Interstitial Lung Disease Program
University of Chicago
Chicago, Illinois

Ralph Panos, MD
Professor of Medicine
VA Pulmonary Section Chief
Associate Clinical Director Pulmonary, Critical Care and Sleep Medicine
University of Cincinnati
Cincinnati, Ohio

Ganesh Raghu, MD
Professor Laboratory Medicine
Division of Pulmonary and Critical Care Medicine
Director, Interstitial Lung Disease / Sarcoid / Pulmonary Fibrosis Program
Medical Director, Lung Transplant Program
University of Washington Medical Center
Seattle, Washington

Glenn D. Rosen, MD
Associate Professor of Medicine
Division Co-Chief, Pulmonary and Critical Care Medicine
Director of the Interstitial Lung Disease Program
Stanford University School of Medicine
Stanford, California

Patricia J. Sime, MD*
Professor of Medicine (Pulmonary and Critical Care), Environmental Medicine, and Oncology
University of Rochester Medical Center
Rochester, New York

David A. Schwartz, MD*
Professor of Medicine
Chairman, Department of Medicine
University of Colorado Medical Center
Denver, Colorado

Moisés Eduardo Selman, MD
Director of Research
Mexican National Institute of Respiratory Diseases
Mexico City, DF Mexico

*Indicates Member of the Research Advisory Committee
Medical Advisory Board
*Indicates Member of the Research Advisory Committee

Charlie Strange, MD
Professor of Pulmonary and Critical Care Medicine
Medical University of South Carolina
Charleston, South Carolina

Robert Strieter, MD*
Professor of Medicine
University of Virginia School of Medicine
Charlottesville, Virginia

Jeffrey J. Swigris, DO, MS
Associate Professor of Medicine
National Jewish Health
Denver, Colorado

Janet Talbert, MS, CGC
Certified Genetic Counselor
Director, Familial Pulmonary Fibrosis Genetic Counseling Program
National Jewish Health
Denver, Colorado
The Pulmonary Fibrosis Foundation recently established the PFF Research Fund to Cure Pulmonary Fibrosis. The goals of the Fund are to support basic research, clinical research, and translational research to help identify new treatments and, ultimately, a cure for PF. In 2012, four recipients will receive awards totaling $200,000.

The PFF Research Advisory Committee, chaired by Jesse Roman, MD, will determine the grant recipients. Applications are scored based on their scientific merit, originality, and responsiveness to the specific purpose of each award category.

**Award Categories**

**Young Investigator Award:** An award of up to $50,000 to be given over a two-year period to encourage young investigators (individuals within five years of completion of their formal training) to maintain and enhance their interest in IPF research during the early stages of their academic career.

**Established Investigator Award:** An award of up to $50,000 to be given over a two-year period to established investigators to explore innovative areas of research that may not yet be eligible for an NIH (or similar) grant.

For details of each award category, including specific criteria for investigator eligibility and an annual calendar of deadlines, please visit www.pulmonaryfibrosis.org/research/PFFgrants.
Meeting Information and Procedures

**Accreditation Statement**
This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the sponsorship of National Jewish Health. National Jewish Health is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

- Approved for maximum of 13 *AMA PRA Category 1 Credits™*
- Approved for maximum of 17.9 Nursing Contact Hours
- Approved for maximum of 15 contact hours CRCE credit

Accreditation details can be found in the Activity Information section of workbook.

**Evaluation Form for CME**
Please remember to complete, sign, and return the evaluation form to the registration desk. **This is the only record National Jewish Health has of your credits.** You should claim only those credits for sessions you actually attended.

**Certificate of Attendance**
For your convenience in reporting CME, CEU, or CRCE, credit you will receive a certificate within 30 days of completion of this activity.

**Name Badge**
Your name badge is your admittance to activities during the conference; it is color coded to denote the session and room in which you are registered to attend. Please wear your badge for the duration of the conference.

**General Session, Exhibit-Poster Hall, and Meals**
You must have a name badge to enter the sessions, Exhibit-Poster Hall, and to participate in meal functions. The Exhibit-Poster Hall is located in Halsted and is open during the following hours:

- **Thursday, December 1st:** 5:00—7:30 PM
- **Friday, December 2nd:** 7:00 AM—5:45 PM
- **Saturday, December 3rd:** 7:00 AM—2:30 PM

Continental breakfasts, lunch, and breaks are for meeting registrants only.

**Cell Phones and Pagers**
Please be courteous to fellow participants and turn your phones and pagers to silent during the lectures.

**“Together We Will Make a Difference in PF” Message Board and Community Map**
The Message Board is a place for conference attendees to leave inspirational and positive messages. We would like participants to connect and collaborate. The Community Map is a visual representation of how the PF community has assembled at the Summit. Mark your hometown with a color-coded pin that indicates your interest in PF. We want all of you to have an impact and “make a difference”! Both are located near the Registration Desk.

**Project PF Action Center**
Share your *Summit* experiences via social media and raise PF awareness, ask your representatives to support the PFREA with a few simple clicks, and participate in the Project PF action for the day.
Oxygen Station
Oxygen refills will be available during Summit hours on Friday, December 2 and Saturday, December 3 to patients with valid prescriptions and who have made an advanced request. Thank you to Lincare for supplying oxygen.

Medical Emergencies
If you are experiencing a medical emergency, please call 911. There is no physician or nurse on site who can legally see or care for a patient with a medical emergency.

Photography, Filming, and Recording of IPF Summit 2011
The IPF Summit 2011 will be photographed, videotaped, and/or recorded in its entirety by staff and third party vendors. The Patient session will be webcast live and on-demand. All sessions will be available post-conference on, but not limited to, the Pulmonary Fibrosis Foundation’s website. Crews will be videotaping and taking still photographs of all sessions, meals, and periphery Summit activities. Conference video, still photographs, and quotes may be used and/or repurposed in promotional materials for the PFF and future IPF Summits, including but not limited to the website, print materials, and social media. All attendees will be asked to sign a Release at registration. For those who do not wish to be filmed or photographed, please be sure to get a red name badge holder at registration for identification.

Disclaimer
Recording of any session is strictly prohibited. The views of the speakers do not necessarily reflect the views of the presenting, partnering, or endorsing organizations. The Pulmonary Fibrosis Foundation, National Jewish Health, and The France Foundation present this information for educational purposes only. The content is provided solely by faculty who have been selected because of recognized expertise in their field. Participants have the professional responsibility to ensure that products are prescribed and used appropriately on the basis of their own clinical judgment and accepted standards of care. The Pulmonary Fibrosis Foundation, National Jewish Health, and The France Foundation assume no liability for the information herein.

If you have any questions or need assistance, please visit the Registration Desk.
IPF SUMMIT 2013
DECEMBER 5–7, 2013

We’ve set the date, now help us choose the location.

Cast your vote at the registration desk or email summit@pulmonaryfibrosis.org with the city of your choice in the subject line.

To receive information about IPF Summit 2013, or to be placed on the pre-registration list, please email summit@pulmonaryfibrosis.org or call 888-733-6741.

SAVE THE DATE
Don’t miss this inspiring event.

Please join us in commemorating the Pulmonary Fibrosis Foundation’s first ten years of research, advocacy, awareness, and support. As we cross our tenth anniversary, we are poised to conquer challenges, expand our reach, and touch the lives of all those affected by pulmonary fibrosis.

FRIDAY, DECEMBER 2, 2011

THE FIELD MUSEUM
1400 SOUTH LAKE SHORE DRIVE

6:30pm RECEPTION
7:30pm DINNER
8:00pm PROGRAM

TICKETS $150 • BUSINESS OR COCKTAIL ATTIRE

EVENT CO-CHAIRS
Former Congressman Brian Baird, Ph.D.
Julie Halston, award-winning Broadway and TV actress and comedienne
Ralph Howard, anchor for the Howard Stern Show, Howard 100 News
Senator Mark Kirk

EVENT EMCEE
Nesita Kwan, reporter and anchor at NBC 5 Chicago News

To purchase tickets please visit the registration desk.

Proceeds will benefit the Pulmonary Fibrosis Foundation’s mission to help find a cure for idiopathic pulmonary fibrosis (IPF), advocate for the pulmonary fibrosis community both locally and in Washington, D.C., promote disease awareness, and provide a compassionate environment for patients and their families.

NEW DECADE
NEW REACH

Together we’ll make a difference in pulmonary fibrosis
Agenda

THURSDAY, DECEMBER 1, 2011

5:00–7:30 PM Welcome Reception and Poster Presentations with hors d’oeuvres
Halsted

FRIDAY, DECEMBER 2, 2011

SCIENTIFIC SESSIONS
PHYSICIANS, RNs, RESEARCHERS, and ALLIED HEALTH PROFESSIONALS

7:00–8:00 AM Registration and Continental Breakfast

8:00–11:15 AM LUNG INJURY AND REPAIR
LEADER: Gregory P. Cosgrove, MD

8:00–8:15 AM Introduction
Daniel M. Rose, MD and Gregory P. Cosgrove, MD

8:15–8:45 AM IPF – What’s Age Got to Do With It?
Joseph Lasky, MD

8:45–9:15 AM A Stressful Environment Leading to Epithelial Injury
Timothy S. Blackwell, MD

9:15–9:45 AM Fibroblasts and Extracellular Matrix: Too Much of a Good Thing?
Eric S. White, MD

9:45–10:15 AM Mediators of the Fibroproliferative Injury−Interactions Between the Epithelium and Fibroblast
Andrew M. Tager, MD

10:15–10:30 AM Visit Exhibits and View Posters

10:30–11:15 AM Roundtable Discussion
LEADER: Gregory P. Cosgrove, MD
PANEL: Timothy S. Blackwell, MD; Joseph Lasky, MD; Eric S. White, MD; Andrew M. Tager, MD; and Glenn D. Rosen, MD
<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Speaker(s)</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>11:15 AM–12:30 PM</td>
<td>GENETICS AND BIOMARKERS</td>
<td>Imre Noth, MD and Christine Kim Garcia, MD, PhD</td>
<td>Leaders: Imre Noth, MD and Christine Kim Garcia, MD</td>
</tr>
<tr>
<td></td>
<td>Introduction</td>
<td>Imre Noth, MD</td>
<td>Defining the Challenges – What Biomarkers Do We Need?</td>
</tr>
<tr>
<td>11:15–11:30 AM</td>
<td>The Genetic Basis of IPF</td>
<td>David A. Schwartz, MD</td>
<td>Leaders: Imre Noth, MD and Christine Kim Garcia, MD</td>
</tr>
<tr>
<td>11:30 AM–NOON</td>
<td>Blood Based Biomarkers to Diagnose and Predict Outcome of IPF</td>
<td>Naftali Kaminski, MD</td>
<td>Leaders: Imre Noth, MD and Christine Kim Garcia, MD</td>
</tr>
<tr>
<td>NOON–12:30 PM</td>
<td>Visit Exhibits and View Posters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12:30–12:45 PM</td>
<td>LUNCH with Kenneth B. Adler, PhD: From Bench to Bedside</td>
<td>Kenneth B. Adler, PhD</td>
<td>From Bench to Bedside</td>
</tr>
<tr>
<td>12:45–1:30 PM</td>
<td>Beyond Rales: Are We Really There Yet?</td>
<td>Christine Kim Garcia, MD, PhD</td>
<td>Leaders: Imre Noth, MD and Christine Kim Garcia, MD</td>
</tr>
<tr>
<td>1:30–1:45 PM</td>
<td>Visit Exhibits and View Posters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1:45–3:15 PM</td>
<td>GENETICS AND BIOMARKERS CONTINUES</td>
<td>Imre Noth, MD and Christine Kim Garcia, MD, PhD</td>
<td>Leaders: Imre Noth, MD and Christine Kim Garcia, MD</td>
</tr>
<tr>
<td>1:45–2:15 PM</td>
<td>Biomarkers for Disease Activity: Designing Drug Studies and Managing Patients</td>
<td>Fernando J. Martinez, MD, MS</td>
<td>Leaders: Imre Noth, MD and Christine Kim Garcia, MD</td>
</tr>
<tr>
<td>2:15–2:30 PM</td>
<td>EPILOGUE</td>
<td>Christine Kim Garcia, MD, PhD</td>
<td>Leaders: Imre Noth, MD and Christine Kim Garcia, MD</td>
</tr>
<tr>
<td>2:30–3:15 PM</td>
<td>Roundtable Discussion</td>
<td>Naftali Kaminski, MD and Fernando J. Martinez, MD</td>
<td>Leaders: Imre Noth, MD and Christine Kim Garcia, MD</td>
</tr>
<tr>
<td>3:15–3:30 PM</td>
<td>Visit Exhibits and View Posters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3:30–5:40 PM</td>
<td>DRUG DEVELOPMENT IN IPF</td>
<td>A. Bruce Montgomery, MD; Harold R. Collard, MD; and Kevin K. Brown, MD</td>
<td>This session is not accredited for CME</td>
</tr>
<tr>
<td>3:30–3:55 PM</td>
<td>Session Overview and Lessons Learned</td>
<td>A. Bruce Montgomery, MD</td>
<td>Leaders: A. Bruce Montgomery, MD; Harold R. Collard, MD; and Kevin K. Brown, MD</td>
</tr>
<tr>
<td></td>
<td>Drug Development in IPF: Lessons Learned from Phase III Clinical Trials</td>
<td>A. Bruce Montgomery, MD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FACILITATOR: Kevin K. Brown, MD</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Speaker: A. Bruce Montgomery, MD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td>Event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 3:55–4:20 PM | Drug Development in IPF: From the Bedside to Approval  
**FACILITATOR:** A. Bruce Montgomery, MD  
**Speaker:** Marianne Mann, MD |
| 4:20–5:40 PM | Drug Development in IPF: Roundtable Discussion  
**FACILITATOR:** Harold R. Collard, MD  
**PANEL:** Ganesh Raghu, MD; Fernando J. Martinez, MD, MS; Williamson Bradford, MD, PhD; A. Bruce Montgomery, MD; Shelia Violette, PhD; Talmadge E. King, Jr, MD; and Ritu S. Baral |
| 5:40–5:45 PM | Session Close  
**Daniel M. Rose, MD** |
| 6:30–10:00 PM| The PFF’s *New Decade, New Reach* Tenth Anniversary Dinner  
The Field Museum |
| 6:30–7:30 PM | Reception                                           |
| 7:30–10:00 PM| Dinner                        |

---

**SATURDAY, DECEMBER 3, 2011**

**SCIENTIFIC SESSIONS**

**PHYSICIANS, RNs, RESEARCHERS, and ALLIED HEALTH PROFESSIONALS**

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>7:00–8:00 AM</td>
<td>Registration and Continental Breakfast</td>
</tr>
</tbody>
</table>
| 8:00–11:45 AM| **CLINICAL SESSIONS**  
**LEADER:** Jeffrey J. Swigris, DO, MS |
| 8:00–9:00 AM | Establishing a Confident Diagnosis  
**Kevin R. Flaherty, MD, MS** |
| 9:00–9:30 AM | Connective Tissue Fibrotic Disorders  
**Aryeh Fischer, MD** |
| 9:30–10:00 AM| Pulmonary Hypertension  
**David A. Zisman, MD, MS** |
| 10:00–10:15 AM| Visit Exhibits and View Posters |
| 10:15–11:30 AM| Treatment Options  
**Kevin K. Brown, MD; Ganesh Raghu, MD; and Marvin I. Schwarz, MD** |
| 11:30–11:45 AM| Questions and Answers  
**All Clinical Session Faculty** |
<table>
<thead>
<tr>
<th>Time</th>
<th>Event Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>11:45 AM–NOON</td>
<td>Visit Exhibits and View Posters</td>
</tr>
<tr>
<td>NOON–1:00 PM</td>
<td>LUNCH: Case Presentations with Master Clinicians</td>
</tr>
<tr>
<td></td>
<td>Kevin K. Brown, MD; Ganesh Raghu, MD; Marvin I. Schwarz, MD; Talmadge E. King, Jr, MD; Aliya N. Husain, MD; and John David Armstrong II, MD, MA</td>
</tr>
<tr>
<td>1:00–1:15 PM</td>
<td>Visit Exhibits and View Posters</td>
</tr>
<tr>
<td>1:15–3:45 PM</td>
<td><strong>UPDATE ON TRANSPLANTATION</strong></td>
</tr>
<tr>
<td></td>
<td>LEADER: Robert B. Love, MD</td>
</tr>
<tr>
<td>1:15–1:45 PM</td>
<td>Recent Trends and Results</td>
</tr>
<tr>
<td></td>
<td>Kenneth R. McCurry, MD</td>
</tr>
<tr>
<td>1:45–2:15 PM</td>
<td>Treatment of Acute Rejections and BOS</td>
</tr>
<tr>
<td></td>
<td>Timothy P. Whelan, MD</td>
</tr>
<tr>
<td>2:15–2:30 PM</td>
<td>Visit Exhibits and View Posters</td>
</tr>
<tr>
<td>2:30–3:00 PM</td>
<td>Ex-Vivo Perfusion</td>
</tr>
<tr>
<td></td>
<td>Robert B. Love, MD</td>
</tr>
<tr>
<td>3:00–3:30 PM</td>
<td>Update on ECMO</td>
</tr>
<tr>
<td></td>
<td>Charles Hoopes, MD</td>
</tr>
<tr>
<td>3:30–3:45 PM</td>
<td>Questions and Answers</td>
</tr>
</tbody>
</table>
Navigating the Summit: Meeting Space Map

THURSDAY, DECEMBER 1, 2011

Marriott Magnificent Mile, 4th Floor

Registration
Halsted (1)

Exhibit Hall
Halsted (1)

Reception
Halsted (1)

Poster Hall
Halsted (1)
Navigating the Summit: Meeting Space Map
FRIDAY, DECEMBER 2, 2011

Marriott Magnificent Mile, 4th Floor

Registration
Halsted (1)

Breakfast and Lunch
Waveland (2)

Breaks
Halsted (1)

Oxygen Refills
Waveland (2)

Speaker Ready (Faculty and Staff Only)
Grace (3)

Sessions for Physicians, RNs, Researchers, and Allied Health Professionals
Marriott Ballroom – Main Floor Seating (4)
Sheffield – Live Feed Seating (5)
Waveland – Open Seating (2)

Exhibit Hall
Halsted (1)

Poster Hall
Halsted (1)
Navigating the *Summit*: Meeting Space Map

SATURDAY, DECEMBER 3, 2011

Marriott Magnificent Mile, 4th Floor

Registration
Halsted (1)

Breakfast and Lunch
Waveland (2)

Breaks
Halsted (1)

Oxygen Refills
Waveland (2)

Speaker Ready (Faculty and Staff Only)
Grace (3)

Sessions for Physicians, RNs, Researchers, and Allied Health Professionals
- Marriott Ballroom – Main Floor Seating (4)
- Sheffield – Live Feed Seating (5)
- Waveland – Open Seating (2)

Sessions for Patients and Caregivers
- Avenue Ballroom – Main Floor Seating (6)
- State – Live Feed Seating (7)

Exhibit Hall
Halsted (1)

Poster Hall
Halsted (1)
Activity Information

Learning Objectives
Following completion of the sessions, participants should be able to:
• Explain the pathophysiology of IPF based on the most current data
• Accurately diagnose IPF using a systematic approach
• Effectively implement key diagnostic procedures, including HRCT scanning and surgical lung biopsy
• Discuss recent evidence for treatments in the management of IPF
• Recognize genetic components of IPF
• Describe the role of lung transplantation in IPF, and the factors that affect candidacy and timing
• Provide patient lifestyle management tools which improve functional status
• Develop a comprehensive approach to the management of IPF, that includes both pharmacologic and non-pharmacologic therapies

Accreditation Information

Accreditation Statement
This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of National Jewish Health and the Pulmonary Fibrosis Foundation.

Designation Statement
National Jewish Health designates this live activity for a maximum of 13 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Nursing Continuing Education Accreditation Statement
Friday Session:
Nursing Continuing Education: National Jewish Health™ is a provider approved by the California Board of Registered Nursing, Provider Number CEP 12724. Attendance at all four scientific sessions during the conference day is accredited for 10.4 Nursing Contact hours. This certificate must be retained by the licensee for a period of four years from the date of this offering.

Saturday Session:
Nursing Continuing Education: National Jewish Health™ is a provider approved by the California Board of Registered Nursing, Provider Number CEP 12724. The entire conference day course is accredited for 7.5 Nursing Contact hours. This certificate must be retained by the licensee for a period of four years from the date of this offering.

Continuing Respiratory Care Education Accreditation Statement
This program has been approved for 15 contact hours (Day 1: 8.25, Day 2: 6.75) Continuing Respiratory Care Education (CRCE) credit by the American Association for Respiratory Care, 9425 N. MacArthur Boulevard, Suite 100, Irving, Texas 75063. Program ID #213362000

Please return your completed evaluation to the registration desk to receive your credit. You should claim only those credits for sessions you actually attended.

*Please note that the “Drug Development in IPF” session is not accredited for CME.
The Pulmonary Fibrosis Foundation presents

IPF SUMMIT 2011
FROM BENCH TO BEDSIDE

CONFERENCE CHAIR
Kevin K. Brown, MD

IPF SUMMIT 2011 PARTICIPATING FACULTY
Thank you to the entire faculty for participating in this educational program.

Kenneth B. Adler, PhD
Professor of Cell Biology
North Carolina State University
Raleigh, North Carolina

John David Armstrong II, MD, MA
Professor, Radiology
National Jewish Health
Denver, Colorado

Ritu S. Baral
Research Analyst, Life Sciences
Canaccord Genuity
New York, New York

Timothy S. Blackwell, MD
Professor of Medicine
Professor of Cancer Biology
Ralph and Lulu Owen Chair in Medicine
Professor of Cell and Developmental Biology
Vanderbilt University Medical Center
Nashville, Tennessee

Williamson Bradford, MD, PhD
Senior Vice President
Clinical Science and Biometrics
InterMune, Inc
Brisbane, California

Kevin K. Brown, MD
Vice Chairman, Department of Medicine
Professor of Medicine
National Jewish Health
Denver, Colorado

Harold R. Collard, MD
Associate Professor of Medicine
Director, Interstitial Lung Disease Program
Division of Pulmonary and Critical Care Medicine
University of California, San Francisco
San Francisco, California

Gregory P. Cosgrove, MD
Associate Professor of Medicine
Department of Medicine
Co-Director, Interstitial and Autoimmune Lung Disease Program
National Jewish Health
University of Colorado
Denver, Colorado

Aryeh Fischer, MD
Associate Professor of Medicine
Autoimmune Lung Center
National Jewish Health
University of Colorado
Denver, Colorado

Kevin R. Flaherty, MD, MS
Associate Director, Fellowship in Pulmonary and Critical Care Medicine
Associate Professor of Medicine
University of Michigan Medical Center
Ann Arbor, Michigan

Christine Kim Garcia, MD, PhD
Associate Professor of Medicine
McDermott Center for Human Genetics
Department of Internal Medicine, Division of Pulmonary and Critical Care Medicine
University of Texas Southwestern Medical Center
Dallas, Texas

Charles Hoopes, MD
Associate Professor of Surgery
Division of Cardiothoracic Surgery
University of Kentucky
Director, Heart and Lung Transplant Program
Director, Heart Mechanical Circulatory Support
University of Kentucky College of Medicine
Lexington, Kentucky
IPF SUMMIT 2011 PARTICIPATING FACULTY

Aliya N. Husain, MD  
Professor of Pathology  
University of Chicago  
Chicago, Illinois

Naftali Kaminski, MD  
Professor of Medicine, Pathology, Human Genetics and Computational Biology  
Director, Dorothy P. and Richard P. Simmons Center for Interstitial Lung Disease  
Director, Lung, Blood and Vascular Center for Genomic Medicine  
Pittsburgh, Pennsylvania

Talmadge E. King, Jr, MD  
Julius R. Krevans Distinguished Professorship in Internal Medicine  
Chair, Department of Medicine  
University of California  
San Francisco, California

Joseph Lasky, MD  
Professor of Medicine  
Section of Pulmonary Diseases  
Co-Director  
Interstitial Lung Disease Clinic  
TCC Program Member  
Tulane University  
New Orleans, Louisiana

Robert B. Love, MD  
Professor of Surgery  
Medical Director, Heart/Lung Transplantation  
Loyola University Medical Center  
Maywood, Illinois

Marianne Mann, MD  
Consultant  
Washington, DC

Fernando J. Martinez, MD, MS  
Professor, Department of Internal Medicine  
Director, Pulmonary Diagnostic Services  
University of Michigan  
Ann Arbor, Michigan

Kenneth R. McCurry, MD  
Surgical Director, Lung and Heart-Lung Transplantation Program  
Department of Thoracic and Cardiovascular Surgery  
Cleveland Clinic  
Cleveland, Ohio

A. Bruce Montgomery, MD  
Cardeas Pharma  
Seattle, Washington

Imre Noth, MD  
Associate Professor of Medicine  
Director, Interstitial Lung Disease Program  
University of Chicago  
Chicago, Illinois

Ganesh Raghu, MD  
Professor Laboratory Medicine  
Division of Pulmonary and Critical Care Medicine  
Director, Interstitial Lung Disease/Sarcoid/Pulmonary Fibrosis Program  
Medical Director, Lung Transplant Program  
University of Washington Medical Center  
Seattle, Washington

Jesse Roman, MD  
Professor of Medicine  
Chairman, Department of Medicine  
Pulmonary, Critical Care and Sleep Disorders Medicine  
University of Louisville  
Louisville, Kentucky

Glenn D. Rosen, MD  
Associate Professor of Medicine  
Division Co-Chief, Pulmonary and Critical Care Medicine  
Director, Interstitial Lung Disease Program  
Stanford University School of Medicine  
Stanford, California

David A. Schwartz, MD  
Professor of Medicine  
Chairman, Department of Medicine  
University of Colorado Medical Center  
Denver, Colorado

Marvin I. Schwarz, MD  
Professor of Medicine Division Co-Head  
University of Colorado  
Denver, Colorado
The Pulmonary Fibrosis Foundation presents
IPF SUMMIT 2011
FROM BENCH TO BEDSIDE

IPF SUMMIT 2011 PARTICIPATING FACULTY

Jeffrey J. Swigris, DO, MS
Associate Professor of Medicine
National Jewish Health
Denver, Colorado

Andrew M. Tager, MD
Assistant Professor of Medicine
Pulmonary and Critical Care Unit
Harvard Medical School
Boston, Massachusetts

Shelia Violette, PhD
Vice President, Research
Stromedix
Cambridge, Massachusetts

Timothy P. Whelan, MD
Associate Professor
Medical University of South Carolina
Charleston, South Carolina

Eric S. White, MD
Associate Professor of Medicine
University of Michigan Health System
Ann Arbor, Michigan

David A. Zisman, MD, MS
Associate Professor
Pulmonary and Critical Care Medicine
University of Southern California
Los Angeles, California
Pulmonary and Critical Care Medicine Consultant
Cottage Hospital
Santa Barbara, California

For Faculty Biographies, please visit the IPF Summit website
www.ipfsummit.org/faculty

Disclosure Information Listed for CME Content Development and Approval Committee and Participating Program Faculty

In accordance with the Accreditation Council for Continuing Medical Education, National Jewish Health requires that all program faculty, content developers, CME approval committee, and medical writers in a position to control the content of this activity are expected to disclose any or not significant financial interest or other relationship with any proprietary entity producing health care goods or services, with the exemption of non-profit or governmental organizations and non-health care related companies. Our goal is to ensure that there is no compromise of the ethical relationship that exists between those in a position to control the content of the activity and those attending the activity and their respective professional duties.

Significant financial interest is defined as receiving, or in the past twelve months having received, a salary, royalty, intellectual property rights, consulting fee, honoraria, ownership interest (eg, Stocks, stock options or other ownership interest, excluding diversified mutual funds), or other financial benefit. Financial benefits are usually associated with roles such as employment, management position, independent contractor (including contracted research), consulting, speaking and teaching, membership on advisory committees or review panels, board membership, and other activities from which remuneration is received or expected.

All CME Educational Activities sponsored by National Jewish Health are reviewed by our faculty CME committee to ensure a balanced and evidence-based presentation. Any potential conflict of interest among program faculty has been identified and resolved according to ACCME guidelines.
Activity Staff Disclosures

The planners, reviewers, editors, staff, or other members at The France Foundation who control content have no relevant financial relationships to disclose.

Faculty Disclosures

<table>
<thead>
<tr>
<th>KEY</th>
<th>A - Advisory Board</th>
<th>E - Employee</th>
<th>O - Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>B - Board of Directors</td>
<td>F - Founder</td>
<td></td>
<td>SP - Speaker</td>
</tr>
<tr>
<td>C - Consultant</td>
<td>I - Investigator</td>
<td></td>
<td>SH - Stockholder</td>
</tr>
</tbody>
</table>

Kenneth B. Adler, PhD
A – BioMarck Pharmaceuticals, Ltd
F – BioMarck Pharmaceuticals, Ltd

John David Armstrong II, MD, MA
Has no significant financial interest to report

Ritu S. Baral
O – InterMune

Timothy S. Blackwell, MD
Has no significant financial interest to report

Williamson Bradford, MD, PhD
E – InterMune

Kevin K. Brown, MD
Has no significant financial interest to report

Harold R. Collard, MD
C – Amira, Fibrogen, Gilead, InterMune
I – Boehringer Ingelheim, Genentech

Gregory P. Cosgrove, MD
Has no significant financial interest to report

Aryeh Fischer, MD
A – Actelion
C – Actelion
I – Genentech, Gilead
SP – Actelion, Gilead

Kevin R. Flaherty, MD, MS
C – Boehringer Ingelheim, Fibrogen, Gilead, GlaxoSmithKline
I – Centocor, ImmuneWorks, InterMune
SP – Boehringer Ingelheim, GlaxoSmithKline, Pfizer
Faculty Disclosures

Christine Kim Garcia, MD, PhD  
Has no significant financial interest to report

Charles Hoopes, MD  
Has no significant financial interest to report

Aliya N. Husain, MD  
Has no significant financial interest to report

Naftali Kaminski, MD  
C – Sanofi Aventis, Stromedix  
I – Gilead Sciences, Inc

Talmadge E. King, Jr, MD  
A – Actelion, Centocor, ImmuneWorks, InterMune  
C – Actelion, AstraZeneca, Centocor, Genzyme, Gilead, GlaxoSmithKline, ImmuneWorks, InterMune, Serono  
I – InterMune

Joseph Lasky, MD  
C – Boehringer Ingelheim, Centocor  
I – InterMune

Robert B. Love, MD  
C – VitaLIFE

Fernando J. Martinez, MD, MS  
A – Actelion, Almirall, Bayer, Centocor, Forest, Gilead, GlaxoSmithKline, Ikaria, Johnson & Johnson, Merck, Novartis, Nycomed, Pearl, Pfizer, Quark  
C – Bayer, GlaxoSmithKline, Nycomed, Sanofi  
O – Associates in Medical Marketing, ePocrates, Stromedix  
SP – Boehringer Ingelheim, CME Incite, The France Foundation, GlaxoSmithKline, HIT-Global, Nycomed

Kenneth R. McCurry, MD  
Has no significant financial interest to report

A. Bruce Montgomery, MD  
E – Gilead

Imre Noth, MD  
A – GlaxoSmithKline  
C – Gilead, ImmuneWorks  
I – AsthmaX, Boehringer Ingelheim, Stromedix  
SP – GlaxoSmithKline

Ganesh Raghu, MD  
C – Actelion, Amira, Bayer, Boehringer Ingelheim, Celgene, Centocor (Johnson & Johnson), Gilead Sciences, GlaxoSmithKline, Stromedix
Faculty Disclosures

Jesse Roman, MD
I – Celgene, Fibrogen, InterMune, ImmuneWorks, NIH and VA, Novartis

Glenn D. Rosen, MD
A – Gilead
C – Celgene Corporation

David A. Schwartz, MD
Has no significant financial interest to report

Marvin I. Schwarz, MD
Has no significant financial interest to report

Jeffrey J. Swigris, DO, MS
C – Genentech, InterMune

Andrew M. Tager, MD
A – Amira Pharmaceuticals
C – Amira Pharmaceuticals, Bristol-Myers Squibb, Stromedix
I – Amira Pharmaceuticals
SP – Astellas Pharma, Merck

Sheila Violette, PhD
E – Stromedix

Timothy P. Whelan, MD
C – ImmuneWorks, InterMune
I – Boehringer Ingelheim, Celgene, Gilead, ImmuneWorks, InterMune

Eric S. White, MD
I – National Institute of Health

David A. Zisman, MD, MS
A – Gilead
I – Boehringer Ingelheim, InterMune
Attendee List (as of November 10, 2011)

Alphabetical by last name

Cynthia Ajilore, Stromedix, Cambridge, MA
Thomas Akey, Concord, NH
Aviva Aloush, St. Louis, MO
Vinny Andaloro, PhD, InterMune, Inc., Phoenix, AZ
Dora Anderson, Albany, NY
Javier Apilanez Tomas, Vigo, Spain
Melissa Ascencio, Marfa, TX
Neelam Azad, Hampton University, Hampton, VA
Masashi Bando, MD, PhD, Jichi Medical University, Tochigi, Japan
Leesa Barone, PhD, Winthrop, MA
Rebecca Bascom, MD, MPH, Penn State Milton S. Hershey Medical Center, Hershey, PA
Shirley L. Becker, Pulmonary Fibrosis Partners, Inc., Newburgh, IN
Heather Behanna, JMP Securities, Chicago, IL
David Berzon, Beachwood, OH
Pauline Bianchi, RN, San Diego, CA
Kelly Blaine, University of Chicago, Riverside, IL
Robert Bloom, MD, Northern Virginia Pulmonary and Critical Care Associates, Annandale, VA
Adam Booth, University of Michigan, Ann Arbor, MI
Melinda Bors, BSN, MA, University of Michigan, Burnsville, MN
Laurie Brewster, Salt Lake City, UT
Kristy Bruins, Baptist Pulmonary & Critical Care Association, Lexington, KY
Andrew Bryant, Vanderbilt University, Nashville, TN
Tedryl Bumpass, Duke Clinical Research Institute, Durham, NC
Linda Burdly, PhD, Biogen Idec, Inc., Cambridge, MA
Jessica Castle, PhD, InterMune, Inc., Longmont, CO
Terrence Chew, MD, ImmuneWorks, Inc., Indianapolis, IN
Jason Chien, Seattle, WA
Alan Cohen, InterMune, Inc., Brisbane, CA
Rany Condos, MD, New York University, New York, NY
Esperet Corinne, PhD, Sanofi-Aventis, Chilly-Mazarin, France
James Couser, MD, Dean Medical Center, Middleton, WI
Csilla Csoboth, MD, PhD, Boehringer Ingelheim, Alameda, CA
Duua Dakhllah, Ohio State University, Columbus, OH
Isabelle Deaemond, San Diego, CA
Daniel Dilling, MD, Loyola University Medical Center, Chicago, IL
Anne Dimmock, Penn State Milton S. Hershey Medical Center, Hershey, PA
Sharon Doherty, RPFT, RCP, AEC, Ingler Memorial Hospital, Tinley Park, IL
Annette Duck, University Hospital of South Manchester, Manchester, United Kingdom
Gwenyth Duhn, BNSC, MSc, Kingston, Canada
Kevin Dushay, MD, Rhode Island Hospital, Providence, RI
Katarine Egressy, MD, University of Wisconsin, Madison, WI
Kristi Esker, Carle Foundation, Teutopolis, IL
Susan Evers, BSN, Overland Park, KS
Elizabeth Fagan, MS, MD, FACP, InterMune, Inc., Brisbane, CA
Jessa Ford, PharmD, InterMune, Inc., Savannah, GA
Attendee List (as of November 10, 2011)

Vicki Friedrich, KSB Hospital, Dixon, IL
Orquidea Garcia, University of Southern California, Los Angeles, CA
Sandra Garfinkel, MSN, RN, Boehringer Ingelheim, Ridgefield, CT
Michael Gilman, PhD, Stromedix, Cambridge, MA
Maureen Gilroy, Olyphant, PA
Ken Glasscock, InterMune, Inc., Brisbane, CA
Tita Gold-Read, North Shore-LIJ, Mount Prospect, IL
Eduard Gorina, MD, InterMune, Inc., Chicago, CA
Cara Gottardi, Northwestern University, Chicago, IL
Elizabeth Gould, ACNP-BC, Boehringer Ingelheim, Chicago, IL
Susan Gravelyn, Ann Arbor, MI
Deborah Green, BSN, Winnebago County Health Department, Rockford, IL
Debby Ham, Silver Spring, MD
Mark Hamblin, MD, University of Kansas Hospital, Overland Park, KS
Jarmilka Hanek, CRA, InterMune, Inc., San Francisco, CA
Gerhard Hannig, Revere, MA
Randall Harris, MD, Mercy Medical Center, Canton, OH
Jeffrey Hartung, PhD, Amira Pharmaceuticals, Inc., San Diego, CA
Jayne Holme, Manchester, United Kingdom
Michael Horton, PharmD, Boehringer Ingelheim, Austin, TX
Howard Huang, Saint Louis, MO
Nick Huang, Loyola University, Chicago, IL
John Huggin, MD, Medical University of South Carolina, Mount Pleasant, SC
Anand Iyer, Hampton University, Hampton, VA
Steven Jackman, MD, Springfield, IL
Jane Jackman, MD, Springfield, IL
Mary Jackson, MD, FRCPC, St. Mary's Hospital, Kitchener, Canada
Yangkin Jegal, PhD, University of Michigan, Ann Arbor, MI
Claude Jourdan Le Saux, PhD, University of Texas Health Science Center, San Antonio, TX
Michael Kamdar, Genoa Pharmaceuticals, San Diego, CA
David Kamp, MD, Hinsdale, IL
Robert Karman, MD, Norton Health Care, Louisville, KY
Michael Kavanaugh, Boehringer Ingelheim, Ridgefield, CT
Sanjay Keswani, Bristol-Myers Squibb, Princeton, NJ
Nasreen Khalil, MD, University of British Columbia, Vancouver, Canada
Hyun Kim, Minneapolis, MN
Gary Kindt, Duluth, MN
Shimon Korish, MD, Celgene Corporation, Warren, NJ
Jonathan Kropski, Vanderbilt University, Nashville, TN
Wade Lange, MS, ImmuneWorks, Inc., Indianapolis, IN
Stephanie Lau, MD, New York University, New York, NY
Joyce Lee, University of California San Francisco, San Francisco, CA
Colm Leonard, University Hospital of South Manchester, Manchester, United Kingdom
Wanqing Liu, PhD, University of Chicago, Chicago, IL
Kathryn Lucas, Boehringer Ingelheim, Ridgefield, CT
Marco Polo Macias, Mexico City, Mexico
Brad Maroni, MD, Stromedix, Cambridge, MA
Alicia Martin, Loyola University, Chicago, IL
Attendee List (as of November 10, 2011)

Eva Mate, Toronto, Canada
Aditi Mathur, Yale University, New Haven, CT
James McArthur, PhD, Synovex, Concord, MA
Kathleen McDougall-Lowe, MPA, Boehringer Ingelheim, Ridgefield, CT
Rob McFadden, MD, FRCPC, London, Canada
Keith Meyer, MD, University of Wisconsin, Middleton, WI
Patricia Mikes, MD, Northwestern University, Chicago, IL
Rebecca Miller, North Shore-LIJ, New Hyde Park, NY
Anne Minnich, PhD, Sanofi-Aventis, Bridgewater, NJ
Sandy Mohan, PhD, InterMune, Inc., Saratoga, CA
Kaci Morgan, RN, National Jewish, Denver, CO
Thomas Munzel, MD, Riverside Regional Medical Center, Williamsburg, VA
Jamie Myers, University of Chicago, Chicago, IL
Anoop Nambiar, San Antonio, TX
George Nauyok, MS, San Francisco, CA
Sean O’Quinn, MPH, MedImmune, Gaithersburg, MD
Thomas O’Riordan, Seattle, WA
Claudio Pasquinelli, Hopewell, NJ
Nina Patel, MD, Columbia University, New York, NY
Daniel Patricia, Bristol-Myers Squibb, Princeton, NJ
James Pearl, MD, Intermountain Health Care/ LDS Hospital, Salt Lake City, UT
Carlos Pereira, MD, Paulista School of Medicine, São Paulo, Brazil
Tamra Perez, BSN, University of Louisville ILD Program, Louisville, KY
Rafael Perez, MD, University of Louisville ILD Program, Louisville, KY
David Perlman, Minneapolis, MN
Jay Peters, MD, University of Texas Health Science Center, San Antonio, TX
Melissa Piper, Ohio State University, Columbus, OH
Seth Porter, PhD, FibroGen, Inc., San Francisco, CA
Jose Portugal, Lima, Peru
Jason Pritchett, Vanderbilt University, Nashville, TN
Sarah Ramey, BS, Duke Clinical Research Institute, Durham, NC
Thomas Richards, PhD, University of Pittsburgh, Pittsburgh, PA
David Riley, MD, Robert Wood Johnson Medical School, New Brunswick, NJ
Pedro J. Marcos Rodriguez, A Coruna, Spain
Tonya Russell, MD, Washington University, Saint Louis, MO
Chris Ryerson, University of British Columbia, Vancouver, Canada
Steven A. Sahn, MD, Medical University of South Carolina, Charleston, SC
Andrea Sambatti, Ingelheim am Rhein, Germany
Lorraine Sandoval, InterMune, Inc., Berkeley, CA
Rozsa Schlenker-Herceg, MD, Boehringer Ingelheim, Ridgefield, CT
Luis Septien, Mexico City, Mexico
Barry Shea, MD, Massachusetts General Hospital, Boston, MA
Anthony Shen, MD, St. Louis, MO
Adrian Shifren, MBCh, Washington University School of Medicine, Saint Louis, MO
Revato Shreeniwas, MD, InterMune, Inc., Brisbane, CA
Paul Simonelli, MD, PhD, Geisinger Health System, Catawissa, PA
Cecilia Smith, DO, The Reading Hospital and Medical Center, West Reading, PA
Christina Soubrane, MD, Sanofi-Aventis, Chilly-Mazarin, France
The Pulmonary Fibrosis Foundation presents

IPF SUMMIT 2011
FROM BENCH TO BEDSIDE

Attendee List (as of November 10, 2011)

Anne Sperling, University of Chicago, Chicago, IL
Krishna Sundar, MD, Utah Valley Pulmonary Clinic, Provo, UT
Mark Surber, PhD, Genoa Pharmaceuticals, San Diego, CA
Stephanie Takahashi, University of Chicago, Chicago, IL
Saito Takefumi, MD, PhD, Ibaraki-higashi National Hospital, Naka-gun, Ibaraki, Japan
Arunabh Talwar, MD, North Shore-LIJ Health System, New Hyde Park, NY
Samuel Tambyraja, Akron, OH
Carolann Tarby, MS, Bristol-Myers Squibb, Princeton, NJ
Leah Tobin, MD, Donal B. Tobin Fund, Roswell, GA
Michael Trabold, PharmD, Moorestown, NJ
Rekha Vij, University of Chicago, Chicago, IL
Guifang Wang, Zhongshan Hospital, Shanghai, China
Alan Watson, PhD, University of Colorado Denver, Aurora, CO
Richard Watson, Columbia Wanger Asset Management, Chicago, IL
Marian Watt, BSCN, Nurse Practitioners of Ontario, Cornwall, Canada
Leslie Watters, MD, Sandy, GA
David Weiner, MD, FACP, FCCP, Beachwood, OH
Peter Werner, MD, FCCP, Wilmette, IL
Lewis Wesselius, MD, Mayo Clinic, Arizona, Scottsdale, AZ
Ralph White, MD, FCCP, Akron General Medical Center, Akron, OH
Elizabeth Wielgus, Schiller Park, IL
David Wilkes, MD, ImmuneWorks, Inc., Indianapolis, IN
Brent Winston, MD, University of Calgary, Calgary, Canada
Ivana Yang, University of Colorado Denver, Denver, CO
Guoying Yu, University of Pittsburgh, Pittsburgh, PA
Richard F. Zegarra, MD, Carmel, IN
Yingze Zhang, University of Pittsburgh, Pittsburgh, PA
Joseph Zibrak, MD, Harvard Medical School, Boston, MA
Xu Zuojun, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing, China

www.pulmonaryfibrosis.org
Pulmonary Fibrosis Foundation Sponsors

The Pulmonary Fibrosis Foundation is grateful to our generous sponsors for helping us fulfill our mission. Their support helps us assist the entire PF community in so many ways. Thank you to our sponsors for assisting us in funding research, advocating on behalf of the PF community, raising awareness and providing education, and playing a critical role in the lives of thousands of patients and families with whom we connect each year. Together we will win the fight against pulmonary fibrosis.

See Summit website for current list.

**EVEREST**
The Bean Family
Mr. and Mrs. Thomas E. Hales

Mr. and Mrs. Charles P. McQuaid

Mrs. Selma Rose

**RAINIER**
Booz | Allen | Hamilton
Phyllis N. Demont
Jenny H. Krauss and Otto F. Krauss
Charitable Foundation Trust

**PROVIDED**

**SHASTA**
Firmicutes

**KILIMANJARO**
InterMune
Daniel M. Rose, MD

**McKINLEY**
PROMEDIOR

**RANIER**

**KILIMANJARO**

**McKINLEY**

**SHASTA**

**EVEREST**

**RAINIER**

**KILIMANJARO**

**McKINLEY**

**SHASTA**

**EVEREST**

**RAINIER**

**KILIMANJARO**

**McKINLEY**

**SHASTA**
Boehringer Ingelheim Pharmaceuticals, Inc
Ridgefield, Connecticut

Boehringer Ingelheim Pharmaceuticals, Inc, the US subsidiary of Boehringer Ingelheim, headquartered in Germany, operates globally in 50 countries with more than 41,500 employees. The company is committed to researching, developing, manufacturing and marketing novel products of high therapeutic value for human and veterinary medicine. For more information please visit http://us.boehringer-ingelheim.com.

Horizon Hospice & Palliative Care
Chicago, Illinois

Horizon Hospice and Palliative Care, Chicago’s first hospice, is a not-for-profit, community-based organization whose mission is to provide comfort for the dying, to preserve dignity at the end of life for all in need of services and to educate the community. Horizon delivers high-quality hospice and palliative care to adults and children throughout Metropolitan Chicago, neighboring counties such as Lake, DuPage and Will.

Ikaria
Hampton, New Jersey

Ikaria is positioned to develop and deliver innovative therapeutics and interventions to meet the needs of critically ill patients. It is our aim to be an indispensable partner to clinicians, providing help and critical care just when patients need it the most. Being part of this lifeline, our desire is to have an impact on the lives of critically ill patients in the hospital and ICU settings. Delivering effective and efficient therapies is our way of serving and supporting these patients.

InterMune
Brisbane, California

InterMune is a biotechnology company focused on the research, development, and commercialization of innovative therapies in pulmonology and fibrotic diseases. In pulmonology, we are focused on therapies for the treatment of idiopathic pulmonary fibrosis (IPF), a progressive and fatal lung disease.

Lincare
Chicago, Illinois

Lincare is dedicated to the service and care our patients, customers, and physicians. Providing the highest level in quality and standards throughout the industry. We are committed to everyone that we deliver and educate through our home care services. We respond to the needs of all patients individually with oxygen systems most appropriate for their condition and lifestyles.
Mayo Clinic  
Rochester, Minnesota

Mayo Clinic is the first and largest integrated group practice in the world. Doctors from every medical specialty work together to care for patients. The entire staff at Mayo Clinic is joined by the philosophy "the needs of the patient come first."

National Jewish Health  
Denver, Colorado

Our mission since 1899 is to heal, discover, and to educate as a preeminent healthcare institution. We serve by providing the best integrated and innovative care for patients and their families; by understanding and finding cures for the diseases we research; and by educating and training the next generation of healthcare professionals to be leaders in medicine and science.

National Jewish Health, the #1 hospital for respiratory care in America, treats patients from all over the country and conducts innovative and groundbreaking research to improve health worldwide.

Pulmonary Fibrosis Foundation  
Chicago, Illinois

The mission of the Pulmonary Fibrosis Foundation (PFF) is to help find a cure for idiopathic pulmonary fibrosis (IPF), advocate for the pulmonary fibrosis community both locally and in Washington, DC, promote disease awareness, and provide a compassionate environment for patients and their families.
Notes
The goals of the IPF Summit are to enhance the clinical and scientific knowledge of pulmonary fibrosis in the medical, research, and patient communities. As part of the Summit, Poster Sessions on basic research, clinical research, translational research, and social science/quality of life will be held in the Halsted Room. The academic posters were evaluated on the following basis:

- Original, new, and significant scientific work
- Major updates and/or significant follow-up on previous research
- Additional definition of previous studies that modify in a major way an understanding of the previous research

**POSTER AWARDS**
Poster awards will be granted to the top three presentations:
- First place: $1,500
- Second place: $1,000
- Third place: $500
- Honorable Mentions (2)

**DISCLOSURES**
All poster presenters were required to disclose any financial relationship with commercial and non-commercial entities, including tobacco entities.

****Industry posters were not subject to peer review and will not be considered for awards.
Impact of Oxidative Stress-Regulated Angiogenesis in Pulmonary Fibrosis

Neelam Azad1, Anand Krishnan V. Iyer1, Vincent Castranova2, Liying Wang2, Yon Rojanasakul3

1Department of Pharmaceutical Sciences, Hampton University, Hampton, Virginia; 2Department of Pharmacological and Pharmaceutical Sciences, West Virginia University, Morgantown, West Virginia; 3Pathology and Physiology Research Branch, National Institute For Occupational Safety and Health, Morgantown, West Virginia

Objectives: Angiogenesis and an aberrant cellular redox state are hallmarks of the pathogenesis of pulmonary fibrosis, but the mechanisms underlying these pathologic alterations are poorly understood. Failure to elucidate and target such critical mechanisms severely limits the effectiveness of current therapeutic efforts against this disease. The objective of this study is to investigate the contribution of oxidative stress-regulated angiogenesis in the pathogenesis of bleomycin-induced pulmonary fibrosis.

Methods: Human lung fibroblasts (CRL-1490), Human umbilical vein endothelial cells (HUVECs), and bleomycin were utilized. Experimental methods used in the study are: CyQUANT® cell proliferation, Trans-well migration, Sircol® collagen assay, Western blotting, Luciferase assay, Spectrofluorometry, Enzyme-linked immunosorbent assay (ELISA), and Tube formation assay.

Results: Bleomycin treatment induced rapid activation of Phosphatidylinositol-3-kinase (PI3K)/Akt and a concomitant increase in fibroblast proliferation and collagen production, characteristics of lung fibrosis. Bleomycin induced Akt phosphorylation (threonine 308/ serine 473), but had minimal effect on total Akt level. Inhibition of Akt phosphorylation by PI3K inhibitors or overexpression of dominant-negative Akt (T308A/S473A) abrogated the fibrogenic effects of bleomycin, suggesting a role of PI3K/Akt in fibrosis. PI3K/Akt activation subsequently led to increased expression of hypoxia inducible factor (HIF)-1α and vascular endothelial growth factor (VEGF) (Figure 1), which contributed to bleomycin-induced fibrogenesis. Consequently, a significant increase in angiogenesis was observed in response to bleomycin (Figure 2). Bleomycin-induced fibrogenesis was dependent on reactive oxygen species (ROS), particularly superoxide anion. Inhibition of ROS by antioxidant enzyme, Mn(III)tetrakis(4-benzoic acid) porphyrin (MnTBAP), a superoxide dismutase mimetic, significantly inhibited the angiogenic pathway (PI3K/Akt→HIF-1α→VEGF) and consequently inhibited bleomycin-induced fibrogenesis and angiogenesis (Figure 2).

Conclusions: Our data provides evidence that oxidative stress-mediated angiogenic pathway significantly contributes to the fibrogenic effects observed with bleomycin. This study purports a novel approach of selectively targeting angiogenesis and oxidative stress, the two major mechanisms that provide sustenance to the damaged tissues and aggravate the pathogenesis associated with pulmonary fibrosis. Establishing the effect of MnTBAP signaling through the angiogenic pathway will be a novel and significant finding that may lay the foundation towards designing more effective therapeutic strategies for the treatment of pulmonary fibrosis.

Acknowledgments: Supported by the NIH/NHLBI grant – 1SC1HL112630-01.
Anand Krishnan V. Iyer1, Neelam Azad1, Yongju Lu2, Liying Wang2, Yon Rojanasakul3

1Department of Pharmaceutical Sciences, Hampton University, Hampton, Virginia; 2Department of Pharmaceutical Sciences, West Virginia University, Morgantown, West Virginia; 3Pathology and Physiology Research Branch, National Institute for Occupational Safety and Health, Morgantown, West Virginia

Objectives: In recent years, nanoparticles such as single-walled carbon nanotubes (SWCNTs) have enjoyed an exponential growth in utility in areas such as electronics and drug delivery. With these applications come unprecedented avenues of human exposure to nanoparticles. Recent reports suggest that SWCNTs exposure leads to pulmonary fibrosis in animals; however, the underlying mechanisms are largely unknown. The objective of this study is to investigate mechanisms involved in SWCNT-induced pulmonary fibrosis and elucidate the role of reactive oxygen species (ROS) and angiogenesis in the process.

Methods: Human lung fibroblasts (CRL-1490), human umbilical vein endothelial cells (HUVECs) and SWCNTs were used. SWCNT-induced fibrogenesis was analyzed by CyQUANT® cell proliferation and Sircol® collagen assays. Western blotting and Enzyme-linked immunosorbent assay (ELISA) were performed to study the role of angiogenic mediators and regulatory proteins. Intracellular ROS production was detected by Spectrofluorometry. Angiogenesis was assessed using Tube formation assay.

Results: SWCNTs induced a strong fibrogenic effect on lung fibroblasts by upregulating collagen expression and enhancing cell proliferation through ROS generation. ROS led to increased activation of p38 mitogen activated protein kinase (MAPK). The p38-MAPK pathway regulated SWCNT-induced fibrogenesis through multiple mechanisms involving transforming growth factor (TGF)-β1 and vascular endothelial growth factor (VEGF). Interestingly, a positive feedback loop was observed between TGF-β1 and VEGF (Figure 1A), with both growth factors contributing significantly to the fibroproliferative and collagen-inducing effects of SWCNTs. This interplay of fibrogenic and angiogenic mediators led to a pronounced angiogenic effect (Figure 1B), suggesting a close association between SWCNT-induced fibrogenesis and angiogenesis.

Conclusions: This study provides evidence that in addition to the fibrogenic effects, SWCNTs are also capable of inducing an angiogenic response (Figure 2). In reporting SWCNT-induced angiogenesis, this study unveils an important physiological process associated with SWCNT-induced lung fibrosis. However, the specific contribution of angiogenesis in either promoting fibrogenesis or playing an anti-fibrogenic role during disease progression remains debatable, and open to further enquiry. Nevertheless, an understanding and elucidation of key mechanisms involved in SWCNT-mediated fibrosis will aid in early detection and prevention of adverse health effects associated with SWCNT exposure.

Acknowledgments: Supported by NIH grant – 1SC1HL112630-01.
Loss of the LRP5 Wnt Co-receptor Protects from Bleomycin-induced Pulmonary Fibrosis

Anna P. Lam, Joseph Sennello, Annette S. Flozak, Susan R. Russell, John Varga, Gökhan Mutlu, GR Scott Budinger, and Cara J. Gottardi

Department of Medicine, Division of Pulmonary and Critical Care Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL 60611

Background: Gene expression profiling studies indicate that signaling pathways required for normal tissue development are dysregulated in pulmonary fibrosis, raising the possibility that fibrosis progresses from a failure to recapitulate normal cellular programming. The Wnt/β-catenin signaling pathway is one such developmental pathway required for cell differentiation and proliferation. While lung tissue from patients with idiopathic pulmonary fibrosis (IPF) show increased nuclear β-catenin as well as expression of Wnt pathway components and down-stream target genes, the extent to which too much or too little Wnt/β-cat signaling causally contributes to lung fibrosis is not firmly established.

Results: Loss of the Wnt co-receptor, LRP5, is protective from bleomycin-induced pulmonary fibrosis in mice. Lungs from LRP5 null mice demonstrate markedly diminished fibrosis by histology, as well as decreased total lung collagen content and bronchoalveolar fluid protein content. Notably, latent and active TGF-β levels are diminished in LRP5 null mice after bleomycin treatment, raising the possibility that Wnt/β-catenin signaling drives fibrogenesis through cross-activating TGFβ signaling. However, forced activation of Wnt/β-catenin signaling in adult lung fibroblasts is not sufficient to upregulate TGF-β mRNA expression or its typical targets, αSMA and collagen, suggesting that in vivo context or cell cross-talk explains the dependence of TGFβ levels on β-catenin signaling.

Conclusions: These findings show that Wnt/β-catenin signaling contributes to bleomycin-induced pulmonary fibrosis in mice. Experiments designed to identify the relevant cell type(s) and degree to which β-catenin signaling promotes fibrogenesis indirectly through TGFβ signaling are ongoing.

Supported by funding from NHLBI K08HL093216 and P30HL101292 (APL) and NIH-GM076561 (CJM).
Imbalance of Th17/Treg Cells Ratio in Patients with Idiopathic Pulmonary Fibrosis

Zuojun XU, Zhiwei LU, Hui Huang, Chunguo Jiang

Department of Respiratory Medicine, Peking Union Medical College Hospital, Peking Union Medical College & Chinese Academy of Medical Sciences, Beijing 100730, China

Corresponding author: xuzj@hotmail.com

Research funding: None

Objective: To investigate the distribution and function of the subtypes of T lymphocyte cells on peripheral blood and BALF in IPF patients.

Methods: Ten IPF patients diagnosed by multidisciplinary review according to consensus criteria were recruited from the Peking Union Medical College Hospital. Ten healthy controls (HC) were recruited from volunteers with the same sex and age. Peripheral blood mononuclear cells (PBMCs) and the lymphocytes of BALF were isolated from the IPF patients and HC. Flow cytometry was used to detect the percentages of Th1, TH2, TH17 and Treg cells in PBMCs from IPF patients and HC respectively. The levels of IFN-γ, IL-4, IL-10, and IL-17A in peripheral blood and BALF were detected through the ELISA. The PBMCs, CD4+CD25-T cells, Treg cells were cultured and stimulated with PHA or rIL-2 in different incubation media (fetal bovine serum(FBSc) and self-serum(SSc)) respectively, and the concentration of the cytokines in supernatant fluid of different incubation media were analyzed with ELISA.

Results:
1. The percentage of Th1 cells in peripheral lymphocyte (PLC) in IPF was lower than that in HC (25.61±6.378% vs 18.38±4.759%, P = 0.009); The percentage of Th2 cells in PLC in IPF was higher than that in HC (2.93±1.520% vs 2.06±0.643%, P = 0.075); The percentage of Th17 cells in PLC in IPF was higher than that in HC (0.21±0.119% vs 1.08±1.339%, P = 0.004); The percentage of Treg cells in CD4+ lymphocyte in IPF was lower than that in HC (2.00±1.132% vs 0.51±0.152%, P = 0.0001).
2. The percentage of Treg cells in CD4+ lymphocyte in the BALF of IPF group was lower than that in HC (1.15±0.451% vs 0.53±0.265%, P = 0.019).
3. The concentration of IFN-γ, IL-10 in blood serum of IPF patients were lower than that in HC (P < 0.05); The concentration of IL-17A in blood serum of IPF patients were higher than that in HC (P < 0.05).
4. The PBMCs and CD4+CD25-T cells were incubated in the different cultures (FBSc and SSc), the concentration of IFN-γ, IL-17A were stimulated with PHA in supernatant fluid of FBSc were higher than that in SSc (P < 0.05).
5. The function of secreting-IL-10 of Treg cells were stimulated with rIL-2 in IPF patients was lower than that in HC (P < 0.05).

Conclusions: Imbalance of Th17/Treg cells ratio may be involved in the pathogenesis of IPF.

Key words: Idiopathic pulmonary fibrosis; T helper type1; T helper type2; T helper type17; regulatory T helper cell
The Significance of Elevated Tumor Markers among Patients with Idiopathic Pulmonary Fibrosis

Victoria Rusanov MD¹, Mordechai R Kramer MD¹, Yael Raviv MD¹, David Shitrit MD²

¹Pulmonary Institute, Rabin Medical Center, Beilinson Campus, Petach Tikva, Israel; Affiliated with Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
²Pulmonary Department, Meir Medical Center, Kfar Saba, Israel Affiliated with Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; Victoria Rusanov: dr.vrusanov@gmail.com

All authors have no conflict of interest

Objectives: Idiopathic pulmonary fibrosis (IPF) is a progressive disease with a 3-year median survival. Lung volume and diffusion capacity at rest are usually used to monitor the clinical course. Due to its high mortality, identification of patients at high-risk is crucial for treatment strategies such as lung transplantation (LTX). This study was designed to determine if tumor markers could accurately characterize disease severity and survival in patients with IPF.

Methods: The study population consisted of 61 patients with progressive IPF, referred for LTX. Pulmonary function tests, cardiopulmonary exercise test, 6-minute walk distance test, and Doppler echocardiogram were assessed at baseline and compared to tumor marker levels. Participants were prospectively followed for at least 25 months to determine the relationship between test parameters and survival. Tumor marker levels were reassessed in LTX patients. Forty-one age and sex matched patients (21 LTX recipients) with chronic obstructive pulmonary disease (COPD) served as controls.

Results: In the IPF group, 9 patients (14.7%) died during follow-up and 20 (32.8%) underwent LTX. Univariate analysis showed correlations between CA 125 and FEV₁ (P = 0.0001). CA 19-9 yielded the best correlations with exercise parameters and PAP. Significant correlation with survival was noted with CA 15-3 (P = 0.04) only. All tumor marker levels decreased significantly following LTX, except CA 125. CA15-3 had the largest decrease (P = 0.001). Among the COPD group, tumor marker levels before LTX were significantly lower compared to the IPF and did not decrease following LTX. No patient in either group developed malignancy.

Table 1: Tumor markers levels before LTX among COPD (n = 41) and IPF patients (n = 61)

<table>
<thead>
<tr>
<th></th>
<th>IPF</th>
<th>COPD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA 125</td>
<td>38.5±34</td>
<td>16±12</td>
<td>0.0001</td>
</tr>
<tr>
<td>CA15-3</td>
<td>92.4±77</td>
<td>16±6.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>CA 19-9</td>
<td>121±28</td>
<td>8.1±3.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>CEA</td>
<td>6.4±9.9</td>
<td>3.8±3.6</td>
<td>0.01</td>
</tr>
</tbody>
</table>
The Significance of Elevated Tumor Markers among Patients with Idiopathic Pulmonary Fibrosis (cont.)

Table 2: Pearson correlation coefficients (r) between the tumor markers and clinical parameters in IPF

<table>
<thead>
<tr>
<th>Tumor marker</th>
<th>r</th>
<th>Age</th>
<th>FVC</th>
<th>FEV1</th>
<th>TLC</th>
<th>CPET</th>
<th>6MWD</th>
<th>PAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA125</td>
<td>0.47</td>
<td>0.03</td>
<td>0.52</td>
<td>0.001</td>
<td>0.001</td>
<td>0.227</td>
<td>0.147</td>
<td>0.08</td>
</tr>
<tr>
<td>CA 15-3</td>
<td>0.04</td>
<td>0.82</td>
<td>0.08</td>
<td>0.04</td>
<td>0.04</td>
<td>0.022</td>
<td>0.05</td>
<td>0.08</td>
</tr>
<tr>
<td>CA 19-9</td>
<td>0.23</td>
<td>0.175</td>
<td>0.243</td>
<td>0.006</td>
<td>0.105</td>
<td>0.125</td>
<td>0.03</td>
<td>0.03</td>
</tr>
<tr>
<td>CEA</td>
<td>0.83</td>
<td>0.120</td>
<td>0.169</td>
<td>0.197</td>
<td>0.158</td>
<td>0.03</td>
<td>0.085</td>
<td>0.008</td>
</tr>
</tbody>
</table>

CPET=Combined pulmonary exercise test; FVC-forced vital capacity; FEV1-forced expiratory volume in 1 sec; TLC-total lung capacity; 6MWD-6 min-walk distance; PAP=Pulmonary artery pressure; Sat=Saturation.

Conclusions: CA 15-3 levels may predict disease severity in IPF. Levels decreased in patients with IPF, but not COPD following LTX and were not associated with malignancy. We suggest that CA 15-3 can be used as a simple, reliable tool to evaluate the disease severity in IPF.

References
Abbreviation List

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATS</td>
<td>American Thoracic Society</td>
</tr>
<tr>
<td>BAL</td>
<td>bronchoalveolar lavage</td>
</tr>
<tr>
<td>CCL-18</td>
<td>CC-chemokine ligand 18</td>
</tr>
<tr>
<td>COPD</td>
<td>chronic obstructive lung disease</td>
</tr>
<tr>
<td>CPET</td>
<td>cardiopulmonary exercise test</td>
</tr>
<tr>
<td>DLCO</td>
<td>carbon monoxide diffusion capacity</td>
</tr>
<tr>
<td>ERS</td>
<td>European Respiratory Society</td>
</tr>
<tr>
<td>IPF</td>
<td>idiopathic pulmonary fibrosis</td>
</tr>
<tr>
<td>IVC</td>
<td>inferior vena cava</td>
</tr>
<tr>
<td>LDH</td>
<td>lactate dehydrogenase</td>
</tr>
<tr>
<td>LTX</td>
<td>lung transplantation</td>
</tr>
<tr>
<td>mPAP</td>
<td>mean PAP</td>
</tr>
<tr>
<td>MVV</td>
<td>maximal voluntary ventilation</td>
</tr>
<tr>
<td>O2P</td>
<td>oxygen pulse</td>
</tr>
<tr>
<td>PF-CVD</td>
<td>pulmonary fibrosis associated with a collagen vascular disorder</td>
</tr>
<tr>
<td>PFT</td>
<td>pulmonary function testing</td>
</tr>
<tr>
<td>RHC</td>
<td>right heart catheterization</td>
</tr>
<tr>
<td>RR</td>
<td>respiratory rate</td>
</tr>
<tr>
<td>RVSP</td>
<td>right ventricular systolic pressure</td>
</tr>
<tr>
<td>SaO2</td>
<td>oxygen saturation</td>
</tr>
<tr>
<td>SP-A</td>
<td>surfactant protein A</td>
</tr>
<tr>
<td>SP-D</td>
<td>surfactant protein D</td>
</tr>
<tr>
<td>VCO2</td>
<td>carbon dioxide production</td>
</tr>
<tr>
<td>Vd/Vt</td>
<td>total ventilation</td>
</tr>
<tr>
<td>VE</td>
<td>minute ventilation</td>
</tr>
<tr>
<td>VO2</td>
<td>oxygen consumption</td>
</tr>
<tr>
<td>VT</td>
<td>tidal volume</td>
</tr>
<tr>
<td>6MWD</td>
<td>6-minute walk distance test</td>
</tr>
</tbody>
</table>
DNA Methylation-Mediated Silencing of the \textit{miR-17--92} Cluster in Idiopathic Pulmonary Fibrosis (IPF)

Duaa Dakhlallah PhD\textsuperscript{1}, Melissa Piper, PhD\textsuperscript{1}, and Clay B. Marsh, MD\textsuperscript{1}

\textsuperscript{1}Department of Internal Medicine/Division of Pulmonary, Allergy, Critical Care, Sleep Medicine; The Ohio State University

**Objectives:** IPF is characterized by ineffective wound repair and increased fibrotic gene expression. We hypothesize that this aberrant gene expression may be due to epigenetic regulation of DNA methylation by microRNAs (miRNAs). Aberrant DNA methylation patterns have been found in lung fibrosis. The \textit{miR-17--92} cluster encodes six miRNAs that target many fibrotic genes as well as DNA methyltransferase-1 (DNMT-1). Previously, we found decreased expression of the \textit{miR-17--92} cluster in human and mouse fibrotic lung tissue, while DNMT-1 was increased. In this study, we explored whether epigenetic mechanisms accounted for the changes in the miRNA and fibrotic gene expression. In addition, we also used the bleomycin model of murine pulmonary fibrosis to examine whether the DNMT inhibitor 5'-aza-2'-deoxycytidine would be an effective therapeutic approach in IPF.

**Methods:** DNA methylation patterns of the \textit{miR-17--92} cluster were determined in human lung fibroblasts, lung tissue from human IPF patients, and lung tissue from bleomycin-treated mice with or without 5'-aza-2'-deoxycytidine treatment. We also examined the expression of DNMT-1, fibrotic genes, and miRNAs by qRT-PCR in the same samples. To determine which miRNAs from \textit{miR-17--92} cluster specifically targeted DNMT-1, we utilized luciferase reporter constructs containing either a wildtype or mutated 3'UTR of DNMT-1.

**Results:** In both human and mouse fibrotic lung tissue samples as well as IPF lung fibroblasts, the \textit{miR-17--92} cluster was hypermethylated compared to normal samples. Four miRNAs (miRs-17,-19b,-20a and-92a) from the \textit{miR-17--92} cluster were found to target DNMT-1. We also found that 5'-aza-2'-deoxycytidine treatment in vitro and in vivo relieved the hypermethylation of \textit{miR-17--92} cluster, with a concordant suppression of fibrotic genes and DNMT-1. In the bleomycin-treated mice, we also observed attenuation of lung fibrosis upon 5'-aza-2'-deoxycytidine treatment even when treatment was initiated after fibrosis had fully developed.

**Conclusion:** Our studies demonstrate that epigenetic changes by the \textit{miR-17--92} cluster and DNMT-1 play a pivotal role in IPF pathogenesis. Furthermore, we uncovered an epigenetic loop between the \textit{miR-17--92} cluster and DNMT-1. In pre-clinical studies, it appears that 5'-aza-2'-deoxycytidine could be a potential therapy for IPF, by reversing \textit{miR-17--92} hypermethylation and thereby repressing fibrotic gene expression.

**Acknowledgments:** This work was supported by grants from NIH/NHLBI/R01 HL102464 (Marsh) and American Thoracic Society (Piper).
Epigenetic Agents to Treat Idiopathic Pulmonary Fibrosis (IPF)

Melissa G. Piper PhD, Leni Moldovan PhD, Duaa Dakhilallah PhD, Clay B. Marsh, MD

Division of Pulmonary, Allergy, Critical Care and Sleep Medicine; The Ohio State University, Columbus, OH

**Objective:** IPF is characterized by ineffective wound repair and increase fibrotic gene expression. Since few genetic mutations are known, we speculated that either transcription factors or DNA methylation of CpG islands in gene promoters are altered in IPF. We found the microRNA cluster, *miR-17~92*, is decreased in human and mouse fibrotic lung tissue which regulates fibrotic gene expression. Since *miR-17~92* contains a CpG islands, we hypothesized that it is regulated epigenetically. Interrogating The Connectivity Map, which is a catalogue of gene signatures from various cells treated with 164 different drugs using IPF gene expression profiles, we sought to identify therapeutic drugs that target epigenetic regulation for IPF.

**Methods:** Expression profiling was performed on IPF lung tissue from patients with various disease severity (n = 23) and normal adjacent tissue from lung cancer biopsies and lungs ineligible for transplantation (n = 6). Differentially expressed genes (DEGs) were determined by having ≥ 1.5 fold change in expression and subjected to analysis using The Connectivity Map. As a model of pulmonary fibrosis, mice were treated with bleomycin for two weeks then with both bleomycin and a DNA methyltransferase inhibitor for two additional weeks. Expression of fibrotic genes and fibrosis were examined in the mice.

**Results:** Comparing IPF lung tissue to control lung tissue, there were 795 downregulated genes and 628 upregulated genes and 106 differentially expressed transcription factors. We selected 52 downregulated and 46 upregulated genes to interrogate The Connectivity Map database. Several of the highest ranked drugs target epigenetic mechanisms. Azacitidine that targets DNA methylation ranked 14th with a favorable correlation score of -0.547. Bleomycin-induced fibrosis was attenuated and fibrotic gene expression was suppressed in mice treated with an analogue of this drug.

**Conclusion:** Our preliminary data suggest that changes in transcription factors and epigenetic regulation occur in IPF. Interrogation of drug catalogues has identified drugs that target epigenetic mechanisms. Using one, we found that inhibiting DNA methylation might be an effective treatment. Currently, we are examining the potential therapeutic benefit of the additional drugs identified in our screen.

**Acknowledgment:** Support was funded from the American Thoracic Society (Piper) and NIH/NHLBI R01 HL102464 (Marsh).
Peptides of CD36 Inhibit the Release of Active Transforming Growth Factor-beta1 (TGF-β1) after Bleomycin (Blm) Induced Pulmonary Injury in the Rat and by Human IPF Lungs, with a Resultant Decrease in Connective Tissue Synthesis in Response to TGF-β1.

Khalil N MD, Liu X MD, Xu Y-D MD, O’Connor D, and Behzad H PhD
Department of Medicine, The University of British Columbia, Vancouver, BC

Objective: To demonstrate that preventing release of biologically active TGF-β1 from cells of fibrotic lungs can prevent connective tissue (CT) synthesis and fibroblast proliferation.

Context: TGF-β1, a fibrotic cytokine is released in a biologically inactive form called latent-TGF-β1 (L-TGF-β1). In a rat model of pulmonary fibrosis induced by intratracheal (IT) Blm, L-TGF-β1 associates with the glycoprotein, thrombospondin-1 (TSP-1), and localizes to the cell by interacting with CD36, which is a receptor for TSP-1, prior to the release of active TGF-β1 and CT synthesis. Ex vivo cultures of IPF lung tissue compared to normal lung, release the active form of TGF-β1. A synthetic peptide of the ectodomain of CD36 (called H1) prevents TSP-1/L-TGF-β1 interaction, release of active TGF-β1, fibroblast proliferation, and CT synthesis in Blm induced pulmonary fibrosis and IPF.

Hypothesis: Peptides related to H1 will be efficacious in preventing the release of active TGF-β1 and CT synthesis in Blm induced fibrosis and in lungs with IPF.

Method: Rats (n = 6-23) received IT normal saline, 1 unit of Blm or Blm with different sizes of peptides of CD36 (called H1, H5, H12). Some rats received H5 intravenously (IV) concomitantly with Blm. The TGF-β1 content of fluid and cells obtained by bronchoalveolar lavage (BAL) was measured by ELISA while Western analysis of lung proteins was used for expression of CT. Explants of human IPF or normal lungs were cultured with the CD36 peptides prior to measurement of TGF-β1 by ELISA, fibroblast proliferation by [H]-thymidine incorporation, and CT synthesis by Western analysis.

Results:

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Blm</th>
<th>H-1</th>
<th>H-5</th>
<th>H-12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat weight on day 7 (% of baseline) (±SEM)</td>
<td>104%±1.0</td>
<td>88%±2.0</td>
<td>98%±0.2</td>
<td>102%±0.5</td>
<td>100%±0.5</td>
</tr>
<tr>
<td>Lung weight (fold above untreated control) (±SEM)</td>
<td>1.15±0.40</td>
<td>2.1±0.086</td>
<td>1.2±0.012</td>
<td>1.5±0.078</td>
<td></td>
</tr>
<tr>
<td>BAL cell# X 10⁶/ml(±SEM)</td>
<td>2.5±0.5</td>
<td>11.5±0.5</td>
<td>6.5±0.25</td>
<td>3.2±0.25</td>
<td>6.25±0.25</td>
</tr>
<tr>
<td>Collagen I (Fold above untreated control) (±SEM)</td>
<td>1.6±1</td>
<td>1.2±0.8</td>
<td>1±1</td>
<td>1.25±0.8</td>
<td></td>
</tr>
<tr>
<td>Collagen III (Fold above untreated control) (±SEM)</td>
<td>1.39±1</td>
<td>1.1±1.2</td>
<td>1±1</td>
<td>0.9±1</td>
<td></td>
</tr>
<tr>
<td>Fibronectin (Fold above untreated control) (±SEM)</td>
<td>1.3±1</td>
<td>1.2±0.8</td>
<td>1.1±8</td>
<td>0.9±0.5</td>
<td></td>
</tr>
<tr>
<td>TGF-β1 in BALF (pgm/10⁶ cells) (±SEM)</td>
<td>17.17±0.44</td>
<td>40.62±5.37</td>
<td>7.62±0.51</td>
<td>11.46±1.29</td>
<td></td>
</tr>
<tr>
<td>p compared control</td>
<td>&lt; 0.001-0.05</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>p compared Blm</td>
<td>NA</td>
<td>&lt; 0.0001-0.05</td>
<td>&lt; 0.0001-0.05</td>
<td>&lt; 0.0001-0.05</td>
<td></td>
</tr>
</tbody>
</table>
Peptides of CD36 Inhibit the Release of Active Transforming Growth Factor-beta1 (TGF-β1) after Bleomycin (Blm) Induced Pulmonary Injury in the Rat and by Human IPF Lungs, with a Resultant Decrease in Connective Tissue Synthesis in Response to TGF-β1 (cont.)

IV administration of H5 improved the rat lung weights and reduced active TGF-β1 from AMs and in the BAL fluid (n = 2). Compared to normal human lungs, IPF lung tissue cultured with the CD 36 peptides generated less active TGF-β1, had decrease in CT synthesis and fibroblast proliferation (n = 4) (P < 0.05).

Conclusion: CD36 peptides could be used to treat idiopathic pulmonary fibrosis.

This work was supported by: CIHR-POP2, NRC-IRAP, and VCHRI
Relative Versus Absolute Change in Forced Vital Capacity in Idiopathic Pulmonary Fibrosis

Christopher J. Ryerson1*, Luca Richeldi2,3*, Joyce S. Lee2, Paul Wolters3, Laura L. Koth1, Brett Ley3, Brett Elicker4, Kirk D. Jones5, Talmadge E. King Jr3, Jay H. Ryu6, Harold R. Collard3

1Department of Medicine, University of British Columbia (Canada); 2Center for Rare Lung Diseases, University of Modena and Reggio Emilia, Modena (Italy); Departments of 3Medicine, 4Radiology, and 5Pathology, University of California San Francisco (USA); 6Department of Pulmonary and Critical Care Medicine, Mayo Clinic, Minnesota (USA).

*These authors contributed equally to this manuscript.

Corresponding author: Christopher Ryerson, MD; Department of Medicine, University of British Columbia – St. Paul’s Hospital, 1081 Burrard St, Ward 8B, Vancouver, Canada, V6Z 1Y6. Phone: 604-806-8818; Fax: 604-806-8839; e-mail: chris.ryerson@hli.ubc.ca.

Funding: HL086516

Faculty disclosure: Dr. Ryerson has received advisory board fees from InterMune (<$5,000).

Objectives: Decline in forced vital capacity (FVC) reliably predicts mortality in patients with idiopathic pulmonary fibrosis (IPF): its use in clinical practice is recommended by current evidence-based guidelines. It is unknown if the method of calculating decline in FVC (relative versus absolute change) impacts its frequency or its ability to predict mortality.

Methods: Consecutive IPF patients from two prospective cohorts were included if they had a baseline and 12 month follow-up FVC. The change in FVC from baseline was calculated in two ways: the relative change in FVC (eg, from 60%-predicted to 54%-predicted) or the absolute change (eg, from 60%-predicted to 50%-predicted). The frequency of a ≥ 10% decline in FVC and its ability to predict two-year transplant-free survival were compared between these two methods. Declines in FVC of ≥ 5% and ≥ 15% were similarly compared. Analyses were performed unadjusted and adjusted for age, gender, oxygen use, baseline FVC, and baseline DLCO.

Results: A total of 142 patients were included. The frequency of a ≥10% decline in FVC was significantly greater using the relative change in FVC method (30% vs. 18%, \( P < 0.001 \)). For ≥ 10% decline, both methods predicted two-year transplant-free survival with similar accuracy, and remained significant predictors after adjusting for baseline clinical and physiological characteristics. The adjusted odds ratios for death or transplant at 2 years were 3.39 for the relative method, and 4.52 for the absolute method, with overlapping confidence intervals. The area under the receiver operating characteristic curve was 0.82 for both methods with adjustment for baseline variables. Time-to-event analyses also showed no significant difference between methods (Figure 1). The absolute change method appeared more predictive for ≥ 5% decline.

Conclusions: The frequency of a decline in FVC is highly influenced by the method used to calculate change in FVC. Using the relative change in FVC maximizes the chance of identifying a ≥ 10% decline in FVC without sacrificing prognostic accuracy. These findings may not hold true for ≥ 5% decline in FVC. These findings have important implications for clinical practice and the design of clinical trials (Figure 2).
Relative Versus Absolute Change in Forced Vital Capacity in Idiopathic Pulmonary Fibrosis (cont.)

FIGURES
Figure 1: Transplant-free Survival Estimates Based On ≥ 10% Decline in FVC.

Kaplan-Meier survival estimates for transplant-free survival are shown for both methods compared between subjects with and without a ≥ 10% decline in FVC at 12 months. Solid lines represent absolute change in %-predicted and dashed lines represent relative change in %-predicted. Median transplant-free survival was 2.35 (relative) and 2.03 (absolute) years for patients with ≥ 10% decline in FVC and 4.71 (relative) and 4.55 (absolute) years for patients without a ≥ 10% decline in FVC.
Relative Versus Absolute Change in Forced Vital Capacity in Idiopathic Pulmonary Fibrosis (cont.)

Figure 2: Impact of Method of Calculating Change in FVC on Sample Size Estimates

Sample size requirements were determined for both methods of calculating change in FVC for a clinical trial using \( \geq 10\% \) decline in FVC as a primary endpoint. Sample size estimates are based on a head-to-head comparison of two therapies, with a baseline decline in FVC of equal frequency and variance compared to our cohort. Samples size estimates are provided for three different effect sizes (20\% relative difference = 0.2, 35\% relative difference = 0.35, and 50\% relative difference = 0.5), and two different power levels (80\% = black bar, 90\% = black plus grey bar).
Clinical Significance of Circulating Autoantibodies in Idiopathic Pulmonary Fibrosis

Joyce S. Lee1*, Eunice J. Kim1*, Kara L. Lynch2, Brett Elicker3, Christopher J. Ryerson4, Tamiko R. Katsumoto1, Anthony Shum1, Paul J. Wolters1, Luca Richeldi6, Kirk D. Jones4, Talmadge E. King, Jr1, Harold R. Collard1

From the Departments of Medicine1, Laboratory Medicine2, Radiology3, and Pathology4 at University of California, San Francisco, CA, USA; the Department of Medicine at University of British Columbia5, Vancouver, Canada; and the Center for Rare Lung Disease6, University of Modena and Reggio Emilia, Modena, Italy.

*These authors contributed equally to this manuscript.

Objective: The significance of autoantibodies in idiopathic pulmonary fibrosis (IPF) is unclear. Our objective was to determine the frequency and clinical significance of autoantibodies in IPF.

Methods: We measured anti-nuclear antibodies using immunofluorescence testing and an extensive panel of autoantibodies typically associated with autoimmune connective tissue diseases or vasculitis in a cohort of well-characterized patients with IPF. The primary control population for autoantibody comparisons was healthy volunteers, ages 50 to 80 years old. We also measured autoantibodies in patients with connective-tissue associated interstitial lung disease (CT-ILD). We analyzed the relationship between autoantibody positivity in IPF and transplant-free survival time.

Results: Twenty-two percent of patients with idiopathic pulmonary fibrosis had at least one positive autoantibody compared to 21% of normals (P-value 0.73). The ANA titers in IPF were similar to that of normals. The autoantibody findings in patients with CT-ILD were consistent with their underlying diagnosis. There were no significant differences in baseline clinical characteristics comparing autoantibody positive and autoantibody negative patients with IPF. The presence of one or more autoantibodies in IPF was associated with longer transplant-free survival time after adjusting for age, gender, forced vital capacity % predicted, and diffusing capacity for carbon monoxide % predicted (HR 0.22, P-value 0.03).

Conclusions: The frequency of autoantibodies was similar between patients with IPF and normals. The presence of at least one autoantibody in subjects with IPF was associated with longer survival time. The IPF autoantibody positive patients described in this study seem to represent a different phenotype of IPF, rather than a clinically-distinct condition such as undifferentiated connective tissue disease.

Funding: NHLBI HL086516, HL097383

Disclosures: I have no disclosures to report.
Genetic Role of the EGFR Pathway in Interstitial Lung Disease (ILD)

Jamie Myers, Snezana Mirkov, Wanqing Liu*

Department of Medicine, The University of Chicago, Chicago, IL, 60637

*The presenter has nothing to disclose.

Funding Resource: This study is supported by the NIH/NHLBI grant (R03 HL097016) (W.L).

Objectives: Although it is now clear that there is a strong genetic basis for the development of ILD, the underlying genetic factors remain incompletely revealed. Recently, the administration of inhibitors for epidermal growth factor receptor (EGFR) has been shown to induce ILD in lung cancer patients with significant ethnic differences. The combination of this observation and evidence from genetically-engineered animal models suggests that genetic variation related to the EGFR pathway may contribute to the development of ILD. Our aims in this study are 1) to test the association between functional alleles in the genes encoding EGFR and its two major ligands, EGF and TGF-alpha (TGFA) and ILD; 2) to investigate the role of expression of these genes in the pathogenesis of ILD.

Methods: DNA and lung tissue samples of ILD patients and normal lung donors were provided by The Lung Tissue Research Consortium (LTRC). Associations between functional polymorphisms (EGF 61A>G, TGFA rs3821262 C>T, EGFR -216G>T and EGFR 497A>G) of the EGFR pathway and idiopathic pulmonary fibrosis (IPF) (n = 84) or other sporadic ILD (n = 143) were tested in a case-control study (control samples, n = 689). Transcription levels of EGF, TGFA and EGFR were compared between ILD (n = 75) and normal lung (n = 17). Since the MUC5B gene was recently identified to confer susceptibility to ILD, its expression was also correlated with that of the EGFR pathway genes.

Results: In the case-control study, the EGF 61A>G polymorphism was significantly associated with ILD as a single phenotype [odd ratio (OR) = 1.34, 95% confidence interval (CI) = 1.08-1.67, P = 0.009]. When considering IPF and combined other ILD as separate phenotypes, this polymorphism was associated with other ILD (OR = 1.4, 95% CI = 1.07-1.83, P = 0.01) but not with IPF. Expressions of EGF and TGFA were significantly higher in ILD compared to the normal lung (P < 0.05). Expression of EGF and TGFA were significantly correlated with that of MUC5B (r = 0.37, P = 0.007; and r = 0.23, P = 0.048, respectively).

Conclusion: Our study suggests that EGFR signaling is activated in the ILD lung, while the intrinsic alteration of the signaling may confer risk to ILD. The pathway may be involved in the pathogenesis of ILD through cross-talking with other pathways, eg, MUC5B.

Acknowledgment: We thank the Lung Tissue Research Consortium (http://www.ltrcpublic.com) and the Translational Research Initiative in the Department of Medicine (TRIDOM) program at the University of Chicago for providing the ILD patients and control samples.
Differential Association between MUC5B and TERT Polymorphisms and Interstitial Lung Disease

Jamie Myers, Snezana Mirkov, Imre Noth, Wanqing Liu*

Department of Medicine, The University of Chicago, Chicago, IL, 60637

*The presenter has nothing to disclose.

**Funding Resource:** This study is supported by the NIH/NHLBI grant (R03 HL097016) (W.L).

**Objectives:** Recent genome-wide genetic studies have identified two polymorphisms, rs2736100 in TERT and rs35705950 at the MUC5B locus, associated with pulmonary fibrosis. However, questions remain whether both polymorphisms equally contribute to the susceptibility to different entities of sporadic interstitial lung disease (ILD), in particular in the same population. The aims of this study are 1) To test and compare the associations of the two polymorphisms with idiopathic pulmonary fibrosis (IPF) and other ILD entities in Caucasian population; and 2) To further define the functional role of the two polymorphisms.

**Methods:** Associations between the two polymorphisms and IPF (n = 84) and other ILD (n = 143) were tested. Transcription levels of MUC5AC and MUC5B, the two genes flanking rs35705950 were correlated with the genotypes in ILD lung tissue (n = 75).

**Main Results:** Both polymorphisms are associated with ILD as a single phenotype [Odds ratio (OR) = 2.22, 95% confidence interval (CI) = 1.69-2.92 for rs35705950 and OR = 1.29, 95%CI = 1.04-1.60 for rs2736100]. When considering IPF and other ILD separately, rs35705950 has a stronger association with IPF (OR = 3.20, 95% CI = 2.1-4.63) than other ILD (OR = 1.76, 95%CI = 1.26-2.48). In contrast, rs2736100 is associated with other sporadic ILD (OR = 1.47, 95%CI = 1.13-1.90) but not IPF (OR = 1.08, 95%CI = 0.78-1.49). Rs35705950 is associated with increased expression of MUC5B but not MUC5AC (r = 0.33, P = 3.49 X10-3). Rs35705950 is also correlated with increased pulmonary function (P < 0.05), and is significantly associated with ILD without airflow obstruction (OR = 3.01, 95%CI = 2.02-4.48).

**Conclusions:** Our study provides additional information supporting the role of these two variants/genes in ILD. The findings suggest that while IPF and other ILD entities share common risk alleles, each of them may also have unique genetic components involved.

**Acknowledgments:** We thank the Lung Tissue Research Consortium (http://www.ltrcpublic.com) and the Translational Research Initiative in the Department of Medicine (TRIDOM) program at the University of Chicago for providing the ILD patients and control samples.
Molecular Pathways Associated with Autoimmunity in Patients with Idiopathic Pulmonary Fibrosis

Vij R¹*, Huang Y¹*, Ma SF¹, Broderick S¹, Strek M¹, White SR¹, Kaminski N², Garcia JGN³, Noth I¹

¹University of Chicago, Chicago, IL, ²University of Pittsburgh, Pittsburgh, PA, ³University of Illinois at Chicago, Chicago, IL

*Equal contribution

Objectives: Guidelines suggest all patients with suspected idiopathic pulmonary fibrosis (IPF) should undergo an evaluation for underlying rheumatologic diseases.¹,² Antinuclear antibody (ANA) titers are serum markers of autoimmunity routinely obtained as nonspecific screening tests for connective tissue diseases (CTD). Elevated ANA titers have been associated with improved survival for some interstitial lung disease patients.³ We hypothesize that IPF patients with elevated autoimmunity have a different gene expression profile compared to IPF patients with low autoimmunity.

Methods: A microarray analysis was performed for subjects with IPF. RNA was extracted from peripheral blood mononuclear cells (PBMC), and hybridized onto an Affymetric Exon 1.0ST array. We compared the gene expression profiles of IPF patients with high (≥ 1:1280) and low (≤ 1:40) ANA titers, matched for age and disease severity. Gene set enrichment analysis (GSEA)⁴ was used to identify upregulated pathways. Genes within these pathways were cross-matched with publicly available microarray data⁵,⁶ from PBMCs of CTD patients to identify candidate genes associated with autoimmunity.

Results: We identified 7 IPF-low ANA and 6 IPF-high ANA subjects. The average age was 65.1±6.4 years for IPF-low ANA and 62.7±12.1 years for IPF-high ANA (P = 0.66). The average composite physiologic index was 46.8±6.8 for IPF-low ANA and 48.3±6.4 for IPF-high ANA (P = 0.70). Unsupervised hierarchical clustering showed a difference in gene expression of these two cohorts (Figure 1). Using GSEA, we identified two overlapping pathways upregulated in IPF-high ANA subjects: Ras protein signal transduction (false discovery rate 0.20) and small GTPase mediated signal transduction (false discovery rate 0.195). Twenty-six genes in the leading edge subsets of both pathways were selected for further analysis, and eleven were also upregulated in patients with CTD (P < 0.05) (Figure 2).

Conclusions: Our results show differences in PBMC gene expression between IPF-high ANA and IPF-low ANA subjects, a subset of which are also upregulated in CTD patients. This suggests that IPF patients with elevated ANA titers may have similarities to CTD patients on a molecular level. Further studies of these genes may elucidate the molecular mechanisms related to autoimmunity in patients with interstitial lung diseases.

Funding: National Institutes of Health, National Heart, Lung, and Blood Institute [Grants HL080513, 1RC1HL099619-01, 1RC2HL1011740]; Pulmonary Fibrosis Foundation (Chicago, IL); and Coalition for Pulmonary Fibrosis (San Jose, CA).

References:
Academic Poster

Molecular Pathways Associated with Autoimmunity in Patients with Idiopathic Pulmonary Fibrosis (cont.)


Figure 1: Heatmap

<table>
<thead>
<tr>
<th>IPF-high</th>
<th>IPF-low</th>
<th>ANA</th>
<th>ANA</th>
</tr>
</thead>
</table>

Figure 2: Gene list

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Gene Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGF2</td>
<td>Fibroblast growth factor 2</td>
</tr>
<tr>
<td>ABCA1</td>
<td>ATP-binding cassette, sub-family A (ABC1), member 1</td>
</tr>
<tr>
<td>ROPN1B</td>
<td>Rhophilin associated tail protein 1B</td>
</tr>
<tr>
<td>LAT</td>
<td>Linker for activation of T cells</td>
</tr>
<tr>
<td>CENTD2 (aka ARAP1)</td>
<td>ArfGAP with RhoGAP domain, ankyrin repeat and PH domain 1</td>
</tr>
<tr>
<td>MFN2</td>
<td>Mitofusin 2</td>
</tr>
<tr>
<td>RHOB</td>
<td>Ras homolog gene family, member B</td>
</tr>
<tr>
<td>SOS1</td>
<td>Son of sevenless homolog 1</td>
</tr>
<tr>
<td>RALBP1</td>
<td>RalA binding protein 1</td>
</tr>
<tr>
<td>ARGHAP4</td>
<td>--</td>
</tr>
<tr>
<td>ARHGAP27</td>
<td>--</td>
</tr>
</tbody>
</table>
The Inhibitory Molecule, BTLA, Regulates Pulmonary Fibrosis in a Mouse Model

Stephenie M. Takahashi, Jesse Williams, Mendy Miller, Yang-Xin Fu, Imre Noth, Anne I. Sperling

University of Chicago, Chicago, IL

Objectives: The argument for a role of the adaptive immune response, and T cells specifically, in IPF can be supported by the literature which has shown that T cells are the predominant mononuclear cell type in the lungs of IPF/usual interstitial pneumonitis (UIP) patients, and that CD3+ T cell density was a significant marker for poor survival (Parra et al, 2007). The effectiveness of T cell activation is influenced by their co-stimulatory receptors and co-inhibitory receptors, which interact with ligands on the antigen presenting cell. The objective of our study is to examine the role of a costimulatory receptor, inducible co-stimulator (ICOS), and a co-inhibitory receptor, B- and T-lymphocyte attenuator (BTLA) in a mouse model of pulmonary fibrosis. We hypothesize that the expression of BTLA and ICOS is involved in or the result of active pulmonary fibrosis.

Methods: BTLA-/-, ICOS-/-, and wild type (B6) mice were treated with intra-tracheal inhalations of bleomycin. The mice were monitored for weight loss and on day 20 the lungs and secondary lymph organs were harvested for flow cytometry expression of costimulatory and activation markers. Lung histology was trichrome stained and scored using a validated scoring system.

Results: All of the mice lost a small amount of weight in the first 24 hours (Figure 1). The wild type B6 control mice quickly gained the weight back, while the ICOS-/- mice lost no more weight after the first 24 hrs. Strikingly, BTLA-/- mice continued to lose weight throughout the experiment. Further, BTLA-/- mice, and to a lesser extent ICOS-/- mice, had increased numbers of lung CD4+ T cells and macrophages compared to controls. Interestingly, both ICOS-/- and BTLA-/- mice had significantly higher levels of lung fibrosis than wild type mice (Figure 2), and BTLA-null mice had extreme levels of fibrosis which may have contributed to the significant weight loss.

Conclusions: These results support the role of altered costimulatory molecules in the progression of IPF implying that these molecules are involved in the pathogenesis of disease progression.

Acknowledgments: This work is supported by RO1-AI46549 to Anne I. Sperling. S. Takahashi is supported by the Research Training in Respiratory Biology T32 HL007605 NIH/NHLBI.
Molecular Phenotyping of the Idiopathic Interstitial Pneumonias Identifies Two Subtypes of Idiopathic Pulmonary Fibrosis

Ivana V. Yang¹,³, Chris D. Coldren¹, Sonia M. Leach², Elissa Murphy¹, Jia Lin², Rachel Burton¹, Steve Groshong¹,³, Carlyne Cool¹,³, Gregory P. Cosgrove¹,³, David Lynch¹,³, Kevin K. Brown¹,³, Marvin I. Schwarz¹,³, Tasha E. Fingerlin⁴, David A. Schwartz¹,³

¹Department of Medicine, University of Colorado School of Medicine, Aurora, CO; ²Center for Genes, Environment and Health, National Jewish Health, Denver, CO; ³Department of Medicine, National Jewish Health, Denver, CO; ⁴Departments of Epidemiology and Biostatistics, Colorado School of Public Health, Aurora, CO

Funding: NHLBI-sponsored Genomic Signatures for Idiopathic Interstitial Pneumonia (RO1-HL095393).

Objectives: The fibrosing idiopathic interstitial pneumonias (IIPs) are classified into distinct subtypes based on a combination of clinical, radiographic, and pathologic criteria. These phenotypic subgroups have proven advantageous in predicting outcome and therapeutic strategy, however a large degree of ambiguity remains. Gene expression profiling has the ability to identify molecular signatures of IIP that can complement our current approaches to phenotyping IIP and begin to represent the dynamic biology in these diseases.

Methods: We collected transcriptional and miRNA profiles on lung tissue from 167 subjects with IIP (119 IPF/UIP, 17 NSIP, 13 uncharacterized fibrosis (UF), 11 RB-ILD, 4 DIP, and 3 COP) and 50 non-diseased controls. Differential expression of individual transcripts and miRNAs was identified using an ANCOVA model incorporating the clinical diagnosis of each subject as well as age, gender, and smoking status.

Results: Our results demonstrate substantial degree of overlap in mRNA and miRNA signatures of clinical subtypes of IIP. However, our results also identify two subtypes of IPF based on a strong molecular signature associated with expression of cilium genes. We demonstrate that elevated expression of cilium genes is associated with more extensive microscopic honeycombing, more fibroblastic foci, higher expression of the airway mucin gene Muc5B, and better survival in an independent cohort of IPF patients. Finally, we also identify miRNAs involved in the regulation of cilia-associated gene expression that contribute to novel molecular subphenotypes of IPF.

Conclusions: Molecular phenotypes of IIP suggest that many of these diseases are related biologically, yet subtypes of IPF/UIP imply unique etiologic and pathogenic events.
Somatic Mutations in the Lungs of Patients with Idiopathic Pulmonary Fibrosis

Ivana V. Yang*1,2, Sonia Leach*1, Julia Turner1, Nathan Kummer1, Joseph Brown1, Elissa Murphy1, Eve Farias-Hesson1, Nicholas Sisneros2, Zhiyong Wang2, Chris Coldren3, Max A. Seibold2, Mick Correll4, Mark Geraci2, Naftali Kaminski5, John Quackenbush4, Frank Sciurba5, Avrum Spira6, David A. Schwartz1,2

*These authors contributed equally to this work

1Center for Genes, Environment and Health, National Jewish Health, Denver, CO; 2Department of Medicine, National Jewish Health, Denver, CO; 3Department of Medicine, University of Colorado School of Medicine, Aurora, CO
4Dana-Farber Cancer Institute and Harvard School of Public Health, Boston, MA; 5Simmons Center for Interstitial Lung Disease and Department of Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA; 6Department of Medicine, Boston University School of Medicine, Boston, MA

Objectives: Idiopathic pulmonary fibrosis (IPF) is a late-onset disease with a poor prognosis (3-5 year survival) characterized by progressive scarring of the interstitium. We hypothesized that similar to lung cancers, somatic mutations are present in the lungs of individuals with IPF and may play a role in disease pathogenesis. To begin to test this hypothesis, we used whole genome sequencing to systematically characterize somatic variation in IPF.

Methods: Whole genome sequencing of DNA from the lung and blood of two individuals with IPF and two non-diseased controls was performed on the SOLiD sequencer. A combination of mate-pair and fragment libraries was used to generate ~30x coverage for the lung and ~20x coverage for the blood DNA. Lung and blood genomes were compared to identify single nucleotide variants (SNVs), copy number variants (CNVs) and structural variants (SVs) present in the IPF lung.

Results: Our analysis of the two IPF and two control paired lung and blood genomes identified 30-50,000 somatic mutations regardless of the disease status. Our analysis identified IPF and non-diseased lung specific single nucleotide variants (SNVs). We are currently analyzing sequence data for CNVs and SVs to identify a set of somatic variants common and unique to the IPF lung genomes.

Conclusions: Our analysis suggests that IPF and non-diseased lung have comparable numbers of somatic variants, suggesting that somatic variation does not play a major role in pathogenesis of IPF. However, our analysis identified IPF- and non-diseased lung specific SNVs.

Funding: NHLBI-sponsored Lung Genomics Research Consortium (RC2-HL101715)
Fibroblast Responses to Decellularized Human Lung Slices Implicate the Extracellular Matrix in Directing Fibroblast Phenotypes

Adam J. Booth, Ashley M. Cornett, Alyssa A. Dreffs, Ryan Hadley, Eric S. White

Division of Pulmonary and Critical Care, Department of Internal Medicine, and Cellular and Molecular Biology Graduate Program, University of Michigan, Ann Arbor, MI

Objectives: Idiopathic Pulmonary Fibrosis (IPF) is characterized by progressive deposition and remodeling of lung extracellular matrix (ECM). As there are no effective therapies for patients with IPF, new insights are needed into the pathogenesis of disease. Altered ECM in IPF patients impairs lung physiology through obliterated pulmonary capillaries, distorted lung architecture, and impaired gas exchange. While physiologic effects of diseased ECM are clear, less is known about its effects on cellular phenotype. Traditionally, ECM-coated plastic dishes have been used to study cellular effects of proteins. However, such coatings do not replicate the 3-dimensional structure or composition of lung matrix in vivo. In contrast, decellularized lung tissue provides an ECM scaffold with relevant structure and composition. We hypothesized that decellularized normal and IPF lung matrix would provide important clues to the effects of ECM on resident cells.

Methods: We optimized a system for decellularizing fresh human lung. Decellularization was confirmed with RT-PCR, Western blot, and immunohistochemistry. Characterization of the intact 3-D structure was verified with SEM, while TEM was utilized to detail ultrastructural differences between normal and IPF ECM. Subsequently, normal lung fibroblasts were cultured in 3-D discs of normal and IPF decellularized matrix to evaluate the role of the ECM in driving phenotypic changes in cells. RT-PCR and Western blot for cellular and ECM proteins were performed on extracted fibroblasts.

Results: Electron microscopy indicates that 3-D tissue structure remains intact and that ECM proteins and proteoglycans are present following decellularization. Atomic force microscopy confirmed the patchy, heterogeneous stiffening of lung seen in the disease. Importantly, normal lung fibroblasts cultured in IPF ECM developed an activated phenotype similar to IPF fibroblasts, whereas normal lung fibroblasts cultured in normal ECM did not.

Conclusions: Decellularized human lung matrices provide a relevant 3-D culture substrate suitable for investigating ECM contributions to basic cell biology and disease pathogenesis. In our preliminary work, IPF lung matrices appear to stimulate fibroblast activation, confirming an active role of ECM in shaping fibrotic responses.
Cognitive Function in Idiopathic Pulmonary Fibrosis (IPF)

Melinda Bors, RN, David Perlman, MD, Deborah Roman, MD, Qi Wang, MS, Hyun Kim, MD, Timothy Whelan, MD

Disclosures: None

Funding: University of Minnesota Medical Foundation Research and Education Fund

Objectives: IPF is a progressive fibrotic disorder resulting in restrictive physiology and impaired gas exchange leading to respiratory failure and death. It is important for patients with IPF to be able to understand and weigh treatment options including participation in clinical trials and complex medical regimens. We hypothesized that there is a measurable difference in cognition between patients with mild to moderate IPF, severe IPF, and an age matched control group without evidence of pulmonary or cognitive dysfunction.

Methods: 49 IPF patients from a subspecialty clinic at the University of Minnesota were divided into two groups of disease severity based on their DLCO. Each group along with the control underwent five different neuropsychological tests, the SF-36, and the Beck Depression Index. The ANOVA F-test examined differences among the group means; to avoid error from multiple comparisons, Turkey-Kramer adjusted P-values were used. We further performed multivariate regression analysis to examine group effect on the TMT B scores, adjusting for gender and age.

Results: Tables 1, 2. Severe IPF group had statistically significantly higher mean TMT B time (135.9 sec, SD = 69.4) than the mild to moderate IPF group and the control group (86.7 seconds [34.8] vs. 83.2 sec [35.4]; P-value 0.004 and 0.008). After adjusting for gender and age, differences were still significant (P values 0.017 and 0.019 respectively). Individuals with severe IPF performed more poorly on the cognitive function tests than individuals with mild to moderate IPF and the control group. The most statistically significant differences were on measures of speeded divided attention (TMT B), processing speeds requiring suppression of a familiar response (Stroop 3), psychomotor speeds (Grooved pegboard – both hands), and to a lesser extent confrontation naming (BNT). In all cases, findings are in a consistent direction with the IPF patients doing worse than normal controls.

Conclusions: These results suggest that individuals with severe IPF have worse cognitive function and are more likely to experience symptoms of depression. These findings expand our understanding of IPF and cognitive function and suggest the need for further research into the mechanisms involved and the development of interventions tailored to address these deficits.

Table 1 – Descriptive Statistics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Severe</th>
<th>Mild-Moderate</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>69 (9.4)</td>
<td>63 (9.6)</td>
<td>66 (10.8)</td>
</tr>
<tr>
<td>FVC</td>
<td>51.58 (13.72)</td>
<td>65.26 (14.60)</td>
<td>NA</td>
</tr>
<tr>
<td>DLCO</td>
<td>19.67 (6.91)</td>
<td>49.03 (14.13)</td>
<td>NA</td>
</tr>
<tr>
<td>O₂ use</td>
<td>100%</td>
<td>61.76%</td>
<td>None</td>
</tr>
</tbody>
</table>

Values listed are means with the standard deviation in parentheses
Cognitive Function in Idiopathic Pulmonary Fibrosis (IPF) (cont.)

Table 2 – Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>Severe</th>
<th>Mild-Moderate</th>
<th>Control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMT-A, in sec.</td>
<td>42.3 (12.9)</td>
<td>33.5 (10)</td>
<td>33.1 (9.8)</td>
<td>0.04</td>
</tr>
<tr>
<td>TMT-B, in sec.</td>
<td>135.9 (69.4)</td>
<td>86.7 (34.9)</td>
<td>83.2 (35.4)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Stroop 1</td>
<td>72 (18.6)</td>
<td>86 (15)</td>
<td>84 (14.4)</td>
<td>0.05</td>
</tr>
<tr>
<td>Stroop 2</td>
<td>49 (18.8)</td>
<td>59 (11)</td>
<td>63 (10.1)</td>
<td>0.02</td>
</tr>
<tr>
<td>Stroop 3</td>
<td>22 (11.7)</td>
<td>30 (9.3)</td>
<td>38 (10.1)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>HVLT – Delayed recall</td>
<td>7.7 (2.4)</td>
<td>7.8 (2.3)</td>
<td>9.7 (1.7)</td>
<td>0.01</td>
</tr>
<tr>
<td>BNT</td>
<td>52.5 (5.4)</td>
<td>55.4 (3.3)</td>
<td>56.7 (2.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Groove board, dominant hand</td>
<td>109.1 (63.4)</td>
<td>74.1 (18.8)</td>
<td>74.5 (17.6)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Groove board, non-dominant</td>
<td>121.3 (63.8)</td>
<td>82.1 (21.9)</td>
<td>78.2 (18.4)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>SF-36, total score</td>
<td>32 (11.4)</td>
<td>59.08 (17.8)</td>
<td>80.33 (12)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>BDI-II</td>
<td>13.7 (7.1)</td>
<td>7.7 (7.1)</td>
<td>5.2 (5.4)</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Values listed are means with the standard deviation in parentheses.
Mimic miR-29 Attenuates Pulmonary Fibrosis Induced by Bleomycin in Mice

Guoying. Yu1, Kusum Pandit1, Jadranka Milosevic1, Rusty L. Montgomery2, Thomas Richards1, Lara J. Chensny, Naftali Kaminski1

1The Dorothy P. and Richard P. Simmons Center for Interstitial Lung Disease, Division of Pulmonary, Allergy and Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA; 2miRagen Therapeutics, Boulder, CO, United States of America

Rationale: Idiopathic pulmonary fibrosis (IPF) is a generally fatal and essentially untreatable interstitial lung disease with poor understanding of the mechanisms and etiology.

Objective: The goal of this study was to determine whether the mimic miR-29 was a therapeutic target for pulmonary fibrosis treatment.

Methods: Eleven months old ICR-F mice were challenged intratracheally with bleomycin at 0.08U/mouse and serially subjected to mimic miR-29 injection (100 mg/kg) via IV at day 3 and day 9 after bleomycin administration. Animal were sacrificed at day 14 and the lungs were harvested for histological and molecular assay.

Results: Administration of mimic miR-29 injection through tail vein significantly increased miR-29a and miR-29b expression in the mouse lungs, but miR-29c was not significant. Hydroxyproline was markedly decreased compared to saline and scramble control with bleomycin induction of fibrosis. Masson trichrome staining verified this result that collagen were accumulated. QRT-PCR analysis showed that mimic miR-29 dramatically downregulated the Col1a1, col3a1, IGF1 and Slug expression. Mimic miR-29 did not affect these gene expressions in saline control group severely compared to bleomycin treatment.

Conclusion: Mimic miR-29 could upregulation of miR-29a and miR-29b expression in mouse lungs and downregulated Col1a1, Col3a1, IGF1 and slug expression, and attenuates lung injury and fibrosis induced by bleomycin. The data suggest that miR-29 should be a potential therapeutic target for pulmonary fibrosis treatment.

Figure 1. Masson Trichrome staining analysis of the mouse lungs.
The Role of a Long Intergenic Non-Coding RNA in Idiopathic Pulmonary Fibrosis

Brenda Juan-Guardela MD, Kusum V. Pandit MBBS, PhD, Caroline Aboud BS, Maria Kapetanaki PhD, Guoying Yu PhD, Naftali Kaminski MD

Dorothy P. and Richard P. Simmons Center for Interstitial Lung Disease, Division of Pulmonary, Allergy and Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA

Objectives: Idiopathic Pulmonary Fibrosis (IPF) is a progressive disease resulting in death over a period of 3-5 years from diagnosis. The only effective treatment for IPF is lung transplant. Recently, a new class of RNAs, long intergenic non-coding RNAs (linc RNA) has been discovered to regulate protein-coding genes by chromatin modification and transcriptional and post-transcriptional regulation. Since IPF is characterized by a distinct gene and microRNA expression, we hypothesized that linc RNAs are differentially expressed in IPF and play a key role in the pathology. Our results will identify new pathways dysregulated in IPF and identify novel targeted therapy.

Methods: We hybridized total RNA from 28 control and 34 IPF whole lungs on to Agilent SurePrint G3 Human 8x60K microarrays. The microarray data was validated by custom TaqMan assays and Northern blot. Linc RNAs were characterized by 5’ and 3’ RACE followed by cloning in suitable vectors. Custom siRNAs were designed to inhibit the linc RNAs in normal human lung fibroblasts.

Results: An intergenic region on chromosome 4 spanning 20 kb is upregulated in IPF lungs which was validated by real-time PCR. Gene-specific PCR of different areas within this 20 kb region was positive indicating the presence of multiple transcripts. Inhibition of the transcripts resulted in increased proliferation. We are currently characterizing the structure and function of these putative linc RNAs.

Conclusions: Considering the known functions of linc RNAs in regulating protein-coding genes, the understanding of this regulatory environment would allow us design interventions that will disturb the pro-fibrotic balance in IPF lungs and potentially cure fibrosis.
Amniotic Fluid Stem Cells as a Novel Strategy to Ameliorate Lung Fibrosis

Orquidea Garcia1,2, Gianni Carraro3, Sargis Sedrakyan3, Laura Perin1,2, David Warburton1,2

1Systems Biology and Disease Graduate Program, The Keck School of Medicine, University of Southern California
2Developmental Biology and Regenerative Medicine Program, The Saban Research Institute, Children’s Hospital Los Angeles

Objectives: We hypothesize that following bleomycin induced lung injury, intravenous (IV) infusion of Amniotic Fluid Stem Cells (AFSC) impacts inflammatory signaling and retards the progression of pulmonary fibrosis. This is a novel yet logical approach for treatment since, in utero, amniotic fluid fills developing lungs and contributes to lung development, maturation, protection and maintenance.

Methods: Female C57Bl/6J mice, 10-12 weeks old, were randomly selected and given 1.5U/kg of bleomycin intratracheally. Cohorts receiving AFSC treatment received 1x10^6 cells IV at either 2 hours or 14 days post bleomycin. Cohorts were sacrificed at 3 days post bleomycin to measure the acute response and at 28 days to measure the fibrotic response. All studies were conducted at the Saban Research Institute, Children's Hospital, Los Angeles.

Results: Mice receiving AFSC at 2 hours versus 14 days post bleomycin exhibited a respective 2-fold versus 1.3-fold reduction in hydroxyproline content at 28 days post injury, when compared to mice receiving no AFSC. Immunofluorescence showed a higher local retention of AFSC in lungs with fibrotic lesions. Immunohistochemistry of the fibrotic regions did not show α-SMA or pro-SPC expression within transplanted AFSC. Cytokine assays performed on tissue lysates of AFSC treated mice during the acute phase showed a statistically significant increase (P < 0.05) in chemotactic signaling molecules CCL1/TCA-3, KC and CCL5 when compared to untreated controls. In bronchoalveolar lavage fluid (BAL) of AFSC treated mice, a statistically significant increase in M-CSF was observed when compared to untreated controls. Western blots of acute phase tissue lysates indicated an upregulation of epithelial cell lineage marker TTF-1 in AFSC treated mice.

Conclusions: AFSC given IV could be used to intervene during both ‘key’ pathogenic phases of inflammation and fibrosis. Infusion of AFSC during the acute phase causes a significant change in the cytokine milieu, both in tissue and BAL, as well as an increased expression of TTF-1. Transplantation of AFSC during the fibrotic phase was characterized by a reduction in both hydroxyproline content and histological fibrosis score.

References: Research funded by NIH NIGMS grant 1R01GM096195: David Warburton, Consortium PI.
Radiographic and Histologic Abnormalities Are Frequently Seen in Asymptomatic Individuals with a Family History of IPF


Vanderbilt University

Funding: HL85317, HL92870, HL85406, HL105479, HL87738, IPFNet CDA

Disclosure: All authors confirm that they have no conflicts of interest pertaining to this abstract and its contents.

Objectives: Familial interstitial pneumonia (FIP) shares many clinical, radiographic, and histologic characteristics with IPF. The genetic cause of FIP is unknown in 85% of cases, but pedigree analysis indicates an autosomal dominant inheritance pattern. First-degree relatives have a 50% chance of sharing a mutant allele with their affected family member, and thus have increased risk of developing disease. These at-risk individuals can provide a cohort to study pathologic mechanisms of FIP prior to development of clinical disease.

Methods: Asymptomatic first-degree relatives of patients with FIP between ages 40-65 are being enrolled in this study. 45 subjects have received a high-resolution CT scan (HRCT) of the chest and a bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsies. BAL cell-count and differentials were obtained, and lymphocyte subsets quantified by flow cytometry. BAL supernatant was analyzed for epithelial injury markers, including Cytokeratin-19 fragments (CK19), CA19-9, and KL-6. Transbronchial biopsies were immunostained for herpesvirus antigens (CMV, EBV) and markers of endoplasmic reticulum (ER) stress (BiP, XBP1).

Results: When combined, 19 out of 45 subjects (42.2%) had abnormalities on either HRCT imaging or transbronchial lung biopsy. Radiographic abnormalities, including interlobular septal thickening and intralobular reticular opacities, were identified in six out of 45 HRCTs (13.3%). Interstitial fibrotic changes were found on transbronchial biopsies from 14 of 45 subjects (31.1%). Differential BAL cell counts were consistent with previously established normals (Average 89.4% Macrophages, 9.0% Lymphocytes, 1.4% Neutrophils, and 0.3% Eosinophils), and flow cytometry did not show differences in T cell subsets between study subjects and normal volunteers. Similarly, BAL markers of epithelial injury did not show any significant differences between study subjects and controls. Immunohistochemical staining was positive for herpesvirus antigens in alveolar epithelium from 18 of 45 individuals at risk for FIP (40.0%), and was positive for ER stress markers XBP1 and/or BiP in 27 of 45 biopsies (61.4%).

Conclusions: Asymptomatic relatives of patients with FIP have detectable radiographic and/or histologic abnormalities that may be consistent with early fibrotic remodeling. Ongoing evaluation is aimed at identifying important epithelial cell pathways (like ER stress) and environmental factors (including herpesviruses) that predict development of clinical disease.

www.pulmonaryfibrosis.org
Herpesvirus Infection Exacerbates Endoplasmic-Reticulum Stress and Acts as A “Second-Hit” in the Development of Lung Fibrosis

Jonathan A Kropski1, Dong-Sheng Cheng1, Vasiliy V Polosukhin1, William E Lawson1,2, Timothy S Blackwell1,2

1Department of Medicine, Division of Allergy, Pulmonary and Critical Care Medicine, Vanderbilt University School of Medicine, Nashville, TN; 2Department of Veterans Affairs Medical Center, Nashville, TN

Funding: HL085317, HL092870, HL105479

Disclosure: All authors confirm that they have no conflicts of interest pertaining to this abstract and its contents.

Objectives: Mutations in surfactant protein C (SFTPC) have been implicated in familial interstitial pneumonia, the familial form of IPF. Endoplasmic reticulum stress (ER-stress) is one mechanism which likely contributes to the development of lung fibrosis. We hypothesized herpesvirus infection, which has been associated with familial and sporadic IPF, could increase ER-stress and lead to lung fibrosis in a mouse model of familial pulmonary fibrosis.

Methods: Transgenic mice with type II alveolar epithelial cell (AEC)-specific, tetracycline-inducible L188Q SFTPC expression were administered doxycycline for one week prior to murine herpesvirus (MHV68) infection and doxycycline was continued throughout the course of experiments. SFTPC and wild-type (WT) C57BL/6 mice were infected with 4x10⁴ PFU of MHV68 by intratracheal injection. Type II AECs were harvested from uninfected mice and infected with MHV68 ex vivo (MOI = 1). Rat lung epithelial (RLE6TN) cells were transfected with human L188Q SFTPC, wild type human SFTPC, or empty vector. RLE6TN cells were then infected with MHV68 (MOI 0.1 to 10) and analyzed at 24 and 48 hours. Cell survival was quantified by Cell Titer Proliferation Assay (Promega). ER-stress was measured by BiP expression and XBP-1 splicing by rt-PCR and western blot. Apoptosis was measured by TUNEL staining. Lung fibrosis was assessed by histology and fibrosis score.

Results: One week after MHV68 infection, SFTPC mice had greater type II AEC apoptosis by TUNEL staining compared to WT mice. At two weeks, there was evidence of increased inflammation in BAL from SFTPC mice. By 3 months after MHV68 infection, SFTPC mutant mice developed significantly greater fibrosis than WT mice. Fibrosis was not observed in uninfected SFTPC mice or WT littermates. In vitro, L188Q SFTPC AECs had decreased survival 48 hours after MHV68 infection compared to controls. Increased BiP expression and greater XBP-1 splicing were found in L188Q SFTPC AECs following MHV68 infection, indicating increased ER-stress.

Conclusions: In combination with a human SFTPC mutation, MHV68 infection causes lung fibrosis in mice. MHV68 exacerbates ER-stress within type II AEC’s, providing evidence for a mechanism by which herpesvirus infection acts as a “second-hit” in the development of pulmonary fibrosis.
Deletion of β-catenin in Type II Alveolar Epithelial Cells Leads to Enhanced Lung Injury and Fibrosis Following Intratracheal Bleomycin

Bryant AJ, Degryse AL, Crossno PF, Tanjore H, Xu XC, Jones BR, Blackwell TS, Lawson WE

Division of Allergy, Pulmonary, and Critical Care Medicine. Vanderbilt University School of Medicine, Nashville, Tennessee

Funding: HL85406, HL105479, HL85317, HL92870, HL87738, IPFNet CDA

Disclosure: All authors confirm that they have no conflicts of interest pertaining to this abstract and its contents.

Objectives: Recent evidence suggests that type II alveolar epithelial cell (AEC) dysfunction is pivotal to the pathogenesis of idiopathic pulmonary fibrosis (IPF). The Wnt/β-catenin pathway is activated in the alveolar epithelium in IPF and is critical for repair of damaged lungs. We hypothesize that dysregulation of β-catenin signaling in type II AECs prevents normal repair following injury, thus leading to greater fibrosis. Our objective was to analyze the role of the Wnt/β-catenin pathway in experimentally induced lung fibrosis.

Methods: We developed a transgenic model with conditional type II AEC deletion of β-catenin after doxycycline administration by crossing 4 transgenic lines: 1) SFTPC.rtTA – reverse tetracycline transactivator under the surfactant protein C promoter, 2) tetO.Cre – Cre recombinase under the tetracycline operator, 3) βcatfl/fl – exons 2-6 of β-catenin flanked by loxP sites, and 4) R26Rosa.Stop.LacZ - STOP cassette flanked by loxP sites upstream of lacZ (gene product βgal). SFTPC.rtTA.TetO.Cre.βcatfl/fl.R26Rosa.Stop.LacZ (STBR) mice and littermate controls were given doxycycline in drinking water (2 grams/liter) and then 1 week later received intratracheal bleomycin (0.04 units). Mice were harvested following bleomycin and lungs analyzed for AEC injury/apoptosis by TUNEL assay, lung inflammation by lavage differential cell counts, degree of fibrosis by evaluation of histology and hydroxyproline assay, and epithelial-mesenchymal transition (EMT) by cell fate mapping strategies.

Results: With doxycycline treatment alone, STBR mice had normal lung architecture. Post-bleomycin, STBR mice had greater mortality, greater AEC death by TUNEL assay at 1 week, and greater lung fibrosis at 3 weeks compared to littermate controls. Differential cell counts in lung lavage were similar in STBR mice and controls at 2 weeks. By immunofluorescence, STBR mice had a decreased percentage of EMT-derived fibroblasts in areas of fibrosis. Lungs from STBR mice had prominent AEC hyperplasia, with many of these cells dual pro-SPC+/CC10+ in areas of fibrosis, a pattern not present in littermate controls.

Conclusion: Bleomycin exposure in mice with conditional deletion of β-catenin in type II AECs results in significantly increased mortality, lung injury, and lung fibrosis. These results demonstrate that the β-catenin pathway in type II AECs is critical to lung repair following injury.
Role of Semaphorin 7a and Lymphocytes in TGF-β1 Driven Lung Fibrosis

Aditi Mathur MD1, Ronald Reilkoff MD, Lynne A. Murray PhD2, Xueyan Peng MD1, Thomas Russell BS1, Hong Peng MD3, Ruth Montgomery PhD1, Albert Shaw MD1, Robert J. Homer MD, PhD1,4, Mridu Gulati MD1, MPH, Jack A. Elias MD1, Erica L. Herzog MD, PhD1

1Yale University School of Medicine Department of Internal Medicine, New Haven, CT, USA; 2MedImmune Ltd, Granta Park, Cambridgeshire, UK; 3South Central University, Changsha, China; 4West Haven VA Medical Center, West Haven, CT, USA.

Objective: Idiopathic Pulmonary Fibrosis (IPF) is associated with Transforming Growth Factor-Beta 1 (TGF-β1) overproduction and accumulation of alternatively activated (M2) macrophages.1 Modulation of CD206+ M2 macrophages is ameliorative in models of pulmonary fibrosis.1,2 Semaphorin-7a (Sema 7a), a glycosylphosphatidylinositol (GPI) anchored membrane protein that regulates monocyte activation, critically regulates experimentally induced lung fibrosis.3,4 We hypothesized that Sema 7a controls macrophage activation in a mouse model of lung fibrosis and in primary cells obtained from patients with IPF.

Methods: All mouse and human experiments were approved by the Yale University School of Medicine. Sema 7a expression was quantified in the blood of IPF patients and normal controls using real time quantitative reverse transcriptase polymerase chain reaction and flow cytometry. The effect of Sema 7a stimulation on CD206 expression by monocytes was assessed in vitro. Mice with a doxycycline inducible, lung specific form of the bioactive form of the human TGF-β1 gene were crossed with mice harboring null mutations of the Sema 7a gene. Bone marrow chimeras were created to determine the cell(s) through which Sema 7a exerts its pro-fibrotic effects. Fibrosis was assessed by Trichrome stains and quantitatively by Sircol assay. M2 macrophage content was determined using flow cytometry for CD206, F4/80, CD11b, and CD11c.

Results: Human: Compared to normal controls, the blood of IPF patients contains increased Sema 7a transcripts which are caused by an increase in Sema 7a-expressing CD19+ and CD4+ cells (Figure 1A). Sema 7a+ CD4+ cells, but not Sema 7a+ CD19+ cells, are highest in those IPF patients with increased CD206+ monocytes who went on to experience rapid clinical decline (Figure 1B). Sema 7a stimulation is sufficient for CD206 expression in normal human monocytes.
Role of Semaphorin 7a and Lymphocytes in TGF-β1 Driven Lung Fibrosis (cont.)

**Murine:** Sema 7a expression on hematopoietic cells is sufficient, but not necessary, for fibrosis and M2 accumulation in the TGF-β1 exposed murine lung (Figure 2 A, B). These effects require CD4 cells and are independent of C19 lymphocytes (Figure 2 C, D).

**Conclusion:** Sema 7a+ CD4+ lymphocytes are predictors of disease progression in human IPF and exert significant pro-fibrotic effects in a mouse model of lung fibrosis.

**Acknowledgments:** NIH HL109033, American Thoracic Society, Pulmonary Fibrosis Foundation

Role of DIO2 in Idiopathic Pulmonary Fibrosis

Guoying Yu, Kazuhisa Konishi, John Tedrow, Kevin F. Gibson, Samuel A. Yousem, Thomas Richards, Lara J. Chensny, Naftali Kaminski

1The Dorothy P. and Richard P. Simmons Center for Interstitial Lung Disease, Division of Pulmonary, Allergy and Critical Care Medicine; 2Department of Pathology, University of Pittsburgh, Pittsburgh, PA, United States of America,

Corresponding author’s email: yug@upmc.edu

Rationale: Idiopathic pulmonary fibrosis (IPF) is a generally fatal and essentially untreatable interstitial lung disease that affects up to 128,000 people annually in the United States. The pathogenic mechanisms and etiology in the majority of patients are poorly understood. To identify candidate genes involved in IPF, we performed microarray analysis of stable and acute exacerbation of IPF lungs compared to normal lungs, and we identified a novel molecule, Iodothyronine Deiodinase 2 (DIO2), may be a potential mediator in IPF initiation and progression.

Methods: RNA was extracted from 83 stable IPF lungs, 28 IPF lungs with acute exacerbation (IPF-AEx), and 60 control lungs and used for hybridization on Agilent gene expression microarrays. Functional analysis of genes was performed with Spotfire and Genomica. Regulation of DIO2 in mRNA level was validated by real-time quantitative reverse transcription polymerase chain reaction. Enzymatic activity assay was performed on the same tissues used for the microarray. ER stresses markers (PERK, ATF6) were measured by qRT-PCR.

Results: Compared with control and emphysema samples, DIO2 gene expression was significantly up-regulated in both stable IPF and IPF-AEx in similar way ($P < 0.05$). To identify the subtler gene expression changes that distinguished IPF-AEx from stable IPF, qRT-PCR data exhibited that DIO2 expression was markedly differentially expressed, DIO2 mRNA in stable IPF was much higher than those in IPF-AEx, which still higher than in normal control ($P < 0.05$). Correspondingly, SECISBP2, DIO2 expression required gene, was drastically down-regulated sequentially in both IPF and IPF-AEx ($P < 0.05$), meanwhile DIO2 upregulation is IPF specific other than emphysema.

Discussion: DIO2 activates thyroid hormone and regulates gene expression by converting the prohormone thyroxine (T4) by outer ring deiodination (ORD) to bioactive 3,3', 5-triiodothyronine (T3). This protein contains selenocysteine (Sec) residues encoded by the UGA codon and its expression requires a sec insertion sequence (SECIS) for the recognition of UGA as a Sec codon rather than as a stop signal and binding protein SECISBP2. Our results demonstrate an increased expression of DIO2 and decreased expression of SECISBP2 in human IPF and IPF-AEx. These differential and impair expressions of DIO2 and SECISBP2 would orchestrate the development and progression of human IPF. Functional assays that DIO2 may prevent alveolar epithelial cells from ER stress in lung. It suggests that DIO2 regulation of thyroid hormone signaling may play a critical role in the development and progression of idiopathic pulmonary fibrosis and should be further investigated as a diagnostic and therapeutic target.

This abstract is funded by: PACCM, University of Pittsburgh
Industry Posters

Industry posters were not subject to peer review.
A Phase One, Open Label, Multi-Dose Study to Evaluate the Safety, Tolerability, and Biologic Effects of Three Doses of IW001 in Patients With Idiopathic Pulmonary Fibrosis (IPF)

K. Rothhaar1*, T. Chew1, S. Frye1, M. Klemsz1,2, W. Lange1, D. Wilkes1,2
1ImmuneWorks Inc, USA; 2Indiana University School of Medicine, USA
katirothhaar@immuneworks.com

Abstract not available at press time.
Interpreting Outcomes in Therapeutic Clinical Trials in Idiopathic Pulmonary Fibrosis (IPF): Benchmarks for Establishing a Clinically Meaningful Benefit

Alan H. Cohen¹, Williamson Z. Bradford¹, Kenneth F. Glasscock¹, Frank Weber²

¹InterMune Inc., Brisbane, CA; ²InterMune International AG, Reinach, Switzerland

Objectives: While the last decade has witnessed an unprecedented number of therapeutic clinical trials in patients with IPF, there is no clear consensus regarding the magnitude of treatment effect that represents a clinically meaningful benefit. In light of the biologic and prognostic similarities between IPF and lung cancer, we conducted a review of therapeutic clinical trials in non-small cell lung cancer (NSCLC) to establish a benchmark for assessing the clinical relevance of the observed treatment effect in recent IPF clinical trials.

Methods: We conducted a literature search to identify all randomized controlled trials evaluating novel therapies in patients with NSCLC. We then selected for inclusion all trials demonstrating a statistically significant treatment effect on either progression-free survival (PFS) or objective response (OR) and compared the reported magnitude of effect with the observed effect of treatment on similar outcomes in 3 Phase III clinical trials evaluating pirfenidone in patients with IPF.

Results: A total of 9 trials involving 12,456 patients with various stages of NSCLC reported a statistically significant treatment effect on PFS. The HR for PFS ranged from 0.60 to 0.83, with 6 of 9 studies reporting a HR > 0.70. The magnitude of effect was consistent with the observed effect of pirfenidone on PFS in 3 Phase III trials in patients with IPF (HR 0.70 [95% CI, 0.56–0.88]; Figure 1). Additionally, a total of 7 trials involving 4,258 patients with NSCLC reported a statistically significant treatment effect on OR. Relative reductions in treatment failure, defined as failure to achieve an OR, ranged between 14% and 22%. The magnitude of effect on OR was consistent with the observed effect of treatment with pirfenidone on objective measures of disease progression in 2 Phase III trials in patients with IPF (Table 1).

Conclusions: The magnitude of effect of pirfenidone on PFS and other objective measures of disease progression in Phase III clinical trials in patients with IPF is consistent with the magnitude of effect in several clinical trials.
Interpreting Outcomes in Therapeutic Clinical Trials in Idiopathic Pulmonary Fibrosis (IPF):
Benchmarks for Establishing a Clinically Meaningful Benefit (cont.)

Table 1. Individual treatment response in randomized controlled trials of therapies for (A) NSCLC and (B) IPF.

<table>
<thead>
<tr>
<th>A</th>
<th>Study</th>
<th>N</th>
<th>Stage</th>
<th>Therapeutic Regimen</th>
<th>Treatment Failure*</th>
<th>Relative Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Le Chevalier et al.</td>
<td>812</td>
<td>III-IV</td>
<td>vinorelbine+cisplatin vs. vindesine+cisplatin</td>
<td>70% vs. 81%</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>Giaccone et al.</td>
<td>332</td>
<td>III-IV</td>
<td>paclitaxel+cisplatin vs. cisplatin+etoposide</td>
<td>59% vs. 72%</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>Bonomi et al.</td>
<td>569</td>
<td>III-IV</td>
<td>paclitaxel+cisplatin vs. etoposide+cisplatin</td>
<td>72% vs. 88%</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>Sederholm et al.</td>
<td>334</td>
<td>III-IV</td>
<td>gemcitabine+carboplatin vs. gemcitabine</td>
<td>70% vs. 89%</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>Mok et al.</td>
<td>1,217</td>
<td>III-IV</td>
<td>gefitinib vs. carboplatin+paclitaxel</td>
<td>57% vs. 68%</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>Reck et al.</td>
<td>1,043</td>
<td>III-IV</td>
<td>bevacizumab+cis+gem vs. cis+gem</td>
<td>66% vs. 80%</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>Lee et al.</td>
<td>161</td>
<td>III-IV</td>
<td>gefitinib vs. docetaxel</td>
<td>72% vs. 92%</td>
<td>22%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B</th>
<th>CAPACITY Trial Outcomes*</th>
<th>Incidence Rates</th>
<th>Relative Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent predicted PVC (Decline ≥10%)</td>
<td>Pirfenidone (n=345)</td>
<td>Placebo (n=341)</td>
<td>30%</td>
</tr>
<tr>
<td>6MWT distance (Decline ≥350 m)</td>
<td>34.8%</td>
<td>47.0%</td>
<td>26%</td>
</tr>
<tr>
<td>Death or disease progression</td>
<td>21.0%</td>
<td>30.0%</td>
<td>26%</td>
</tr>
</tbody>
</table>

*Failure to achieve a protocol-defined objective response (either partial or complete response)

References

Disclosures: All authors are salaried employees and stock holders in InterMune, Inc.
Unintentional Chronic Exposure to Ultrafine Particles (UFPs) During Cooking May Result in Idiopathic Pulmonary Fibrosis (IPF).

Author: Jamson S. Lwebuga-Mukasa, MD, PhD. Founder, President and CEO, Respiratory and Environmental Exposure Consultants LLC, Getzville, NY 14068. E-mail: jlwebuga@buffalo.edu

Introduction: UFPs are particles less than 200 nanometers in diameter. They cause intense inflammation without a lower concentration threshold. Unintentional exposure to UFPs occurs during cooking. Many homes have cooking stoves that are not vented to the outside, or have hoods that are not routinely used. Air exchange is further worsened by tight buildings which are intended to conserve energy. Our objective was to determine whether exposure to UFPs in poorly ventilated homes may contribute to IPF.

Methods: UFPs were measured with TSI UFP monitor (TSI, Instruments) before turning on a gas or electric cooking stove (baseline) in 23 kitchens for 15 minutes without any food on the stove, with hood fan off. The TSI monitor was placed one meter away from the stoves. The stoves were then turned on to “high” for 15 minutes, without any food on the burner and continued measuring UFP concentrations. The burners were turned off for 30 minutes while monitoring was continued, after which an air purifiers were turned on. High resolution microscopy was used to identify UFPs in IPF lung biopsies.

Results: Baseline UFP counts ranged between 3,000 to 5,000 particles per cc (ppcc). Running air purifiers decreased the counts to 500 ppcc within 20 minutes but counts rose to baseline when air purifiers were turned off. UFP concentration rose to 350,000 ppcc; the highest counts (greater than 500,000 ppcc) were recorded in an urban home where the occupant had complained of “not feeling right” in the home. UFP concentrations remained elevated three hours after turning off the burners but decreased within 20 minutes with air filtration. High resolution microscopy of IPF lung biopsies revealed UFPs in alveolar basement membranes, fibrotic areas of the lung.

Conclusions: Electric or gas stoves release UFPs that cause inflammation in lungs and other organs. High UFPs levels are sustained for long periods following cooking and can be decreased by air filtration. IPF belongs to a group of inflammatory diseases related to UFP exposure and may be prevented by improved ventilation.

Acknowledgments: Research funded by Respiratory and Environmental Exposure Consultants LLC, Getzville, NY.
The Effects of Recombinant Human Pentraxin-2, (PRM-151), on Circulating Fibrocytes in Idiopathic Pulmonary Fibrosis (IPF)

JA Getsy1, D Harper1, M Levy2, J Burggraaf2, M Moerland2, I de Visser2, M Wijsenbeek1, B van den Blink1, K Gumbhir-Shah4, A Cohen2, M Lupher Jr1

1Promedior - Malvern, PA/US, 2Center for Human Drug Research - Leiden/NL, 3Erasmus Medical Center - Rotterdam/NL, 4PharmaMed Resources - Basking Ridge, NJ/US

Introduction: Pentraxin-2 (PTX-2) is a naturally occurring protein that constitutively circulates in blood and plays a critical role in regulating innate immune cells including monocyte derived cells (fibrocytes, macrophages, dendritic cells) and myofibroblasts. Pre-clinical studies have shown that inducing an elevated level of PTX-2 systemically or locally at a site of injury can reduce inflammation and prevent production of excess scarring and progression of fibrosis by inhibiting the differentiation of peripheral mononuclear precursor populations to fibrocytes and profibrotic macrophages. Elevated levels of circulating fibrocytes have been correlated with disease severity and mortality in patients with IPF. PRM-151 is a recombinant human PTX-2 being developed to prevent, treat, and reduce established fibrosis. Here, we investigated the safety, pharmacokinetics, and pharmacodynamics of PRM-151 in healthy volunteers and pulmonary fibrosis patients.

Methods: A randomized, double masked, placebo controlled study was initially performed in 26 healthy normal volunteers to establish safety, pharmacokinetics, and preliminary pharmacodynamics. Single doses from 0.1 mg/kg to 20 mg/kg were administered. After completion of dosing of the healthy volunteers, three patients with idiopathic pulmonary fibrosis were administered a single dose of 10 mg/kg IV to confirm the safety, pharmacokinetics, and to assess the pharmacodynamic effects of PRM-151 on serum cytokine and fibrocyte biomarkers.

Results: Single doses of PRM-151 up to 20 mg/kg were safe and well tolerated in both healthy volunteers and IPF patients. There were no dose limiting adverse events and all adverse events were self limiting. No severe or serious adverse events occurred. At the highest dose tested, PRM-151 levels increased dose dependently in healthy volunteers and raised baseline PTX-2 levels at least tenfold. The t1/2 was 30 hours. The safety and pharmacokinetics of the 10 mg/kg dose were comparable in IPF patients with a 7 to 10 fold increase in baseline circulating levels of PTX-2 after administration of a single 10 mg/kg dose. Analysis of biomarkers comparing healthy volunteers and IPF patients indicated that elevated serum IL-6 levels decreased up to 50% (P < 0.05) measured 48 hours after PRM-151 dosing which was the last sampling time point. A 50% reduction of CD45+/collagen-1+ fibrocytes within peripheral blood of all IPF patients was observed at 24 hours.

Conclusions: The results of this study indicate that PRM-151 decreases circulating IL-6 and CD45+ collagen-1+ fibrocytes in peripheral blood of IPF patients. Further study with multiple doses of PRM-151 in IPF patients is needed to confirm these potentially beneficial effects.
SAR156597: An Innovative Bispecific IL-4/IL-13 Antibody as a Potential Treatment for Idiopathic Pulmonary Fibrosis


Sanofi Pharmaceuticals, Bridgewater, New Jersey and Chilly-Mazarin, France

Objectives: Idiopathic pulmonary fibrosis is a rare and very severe disease of unknown etiology that has extremely limited therapeutic options and a mean survival time of only 3 years. Interleukin (IL)-4 and IL-13 have been implicated as mediators of lung fibrosis through effects on fibroblasts, epithelial cells, and macrophages. We are developing SAR156597, an innovative bispecific antibody that targets both IL-4 and IL-13. By neutralizing both these cytokines, we believe that SAR156597 will efficiently block profibrotic pathways downstream of the IL-4/IL-13 receptors. SAR156597 promises to be a novel treatment for idiopathic pulmonary fibrosis, and potentially other fibrotic indications with the same underlying mechanisms.

Methods and Results: The design of SAR156597 combines Fv domains of humanized anti-IL-4 and anti-IL-13 antibodies into a tetravalent, bispecific format. SAR156597 has a balanced affinity for IL-4 and IL-13, and is able to bind both cytokines simultaneously until all binding sites are saturated. SAR156597 inhibited IL-4 and IL-13-induced Stat6 phosphorylation in human monocytes in vitro (IC50 values were 1 and 2 nM respectively), and IL-4 and IL-13-induced activation of human IPF pulmonary fibroblasts in vitro (including induction of eotaxin, IL-6, and lysyl oxidase) (IC50 values were 3 to 8 nM). In a cynomolgus monkey model of asthma, used to demonstrate pulmonary activity in vivo, SAR156597 (2.5 mg/kg, i.v.) significantly suppressed airway hyperresponsiveness and serum IgE.

Conclusion: SAR156597 is an innovative bispecific antibody that neutralizes IL-4 and IL-13 and promises to suppress profibrotic activities of lung fibroblasts, epithelial cells and macrophages. SAR156597 has entered early clinical development for the treatment of idiopathic pulmonary fibrosis. A clinical study of biomarkers will assess the natural history of the disease, and will be used to select an appropriate population for studies of the biological activity and efficacy of SAR156597.
Clinical Development of STX-100, a Humanized anti-αvβ6 Antibody, for Patients with Idiopathic Pulmonary Fibrosis

Bradley J. Maroni, MD1, Kevin Gibson, MD2, Ruth E. Stevens, PhD, MBA3, Shawna Bredek, BS4, Cynthia Ajilore, AS1, Michael Gilman PhD1, Timothy Rice, BS, MBA1, Shelia M. Violette, PhD1

1Stromedix Inc., Cambridge, MA; 2University of Pittsburgh, Pittsburgh, PA; 3Camargo Pharmaceutical Services, Cincinnati, OH; 4CTI, Clinical Trial and Consulting Services, Cincinnati, OH

Introduction: STX-100, a humanized anti-αvβ6 antibody, is currently in clinical development in a Phase 2a trial in patients with idiopathic pulmonary fibrosis (IPF). The αvβ6 integrin is a key mediator of TGF-β activation and plays an important functional role in promoting and maintaining fibrogenesis and epithelial injury, providing a novel and relevant target for this disease. Since αvβ6 is expressed at low levels in normal tissue and upregulated on injured epithelium in disease, blocking this integrin provides a targeted approach for localized suppression of TGF-β.

Methods: We previously carried out a Phase 1 trial with STX-100 in normal healthy volunteers. This was a randomized, double-blind, placebo-controlled, single-dose, dose-escalation study evaluating the safety, tolerability, and pharmacokinetics (PK) of STX-100. Forty subjects were enrolled into five ascending-dose cohorts (6 active: 2 placebo subjects per cohort), received a single subcutaneous dose of STX-100 (range: 0.003 to 0.3 mg/kg) or placebo, and were monitored for three months after dosing.

Results: The mean age of the participants was 32 years (range: 19-48), 58% were female, and 90% were Caucasian. STX-100 was well tolerated; no serious adverse events were reported nor was there evidence of a dose-dependent effect on adverse events or laboratory parameters across the five cohorts. The half-life of STX-100 averaged 6 days with maximal concentration observed 5 days post-dosing. Area under the serum concentration-time curve (AUC) and maximal serum concentration (Cmax) exhibited dose-proportionality.

Conclusion: STX-100 was well tolerated following a single subcutaneous dose in healthy volunteers. A Phase 2a multicenter trial in IPF patients is underway to evaluate the safety, tolerability, PK, and immunogenicity of STX-100, as well as the expression of pharmacodynamic biomarkers of STX-100 activity in bronchoalveolar lavage (BAL) cells. The BAL biomarkers will include phosphorylated SMAD2 and TGF-β-inducible genes, as markers of STX-100-mediated inhibition of TGF-β activity in the lung. This study includes four ascending dose cohorts (6 active: 2 placebo subjects per cohort) who will receive eight weekly subcutaneous doses of either STX-100 (range: 0.015 to 1.0 mg/kg) or placebo.
Identification of Biomarkers to Monitor the Activity of STX-100, a Humanized anti-αvβ6 Antibody, in a Phase 2a Trial in Idiopathic Pulmonary Fibrosis

Shelia M. Violette, PhD¹, Dean Sheppard, MD², Ivan Rosas, MD³, Mehrdad Arjomandi MD², Timothy Rice, BS, MBA¹, Michael Gilman, PhD¹, Naftali Kaminski, MD⁴, Antje Prasse, MD, PhD⁵, Bradley J. Maroni, MD¹

¹Stromedix Inc., Cambridge, MA; ²University of California San Francisco, San Francisco, CA; ³Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, ⁴University of Pittsburgh, Pittsburgh, PA, ⁵University Medical Center Freiburg, Germany

Introduction: The αvβ6 integrin is a key mediator of TGF-β activation and plays an important functional role in promoting and maintaining fibrogenesis and epithelial injury. Previous studies have demonstrated that blocking this integrin effectively inhibits TGF-β activation, epithelial injury, and tissue fibrosis in multiple disease models. A humanized antibody to αvβ6 (STX-100) is currently in clinical development in a Phase 2a trial in patients with idiopathic pulmonary fibrosis (IPF). We describe the identification of bronchoalveolar lavage (BAL) biomarkers that will be used to monitor STX-100 activity in this Phase 2a trial.

Methods: BAL cells were isolated from cynomolgus monkeys at baseline and after eight weekly doses of STX-100 (0.1, 0.3, 1.0, 3.0, and 10 mg/kg). Cells were processed and evaluated for phosphorylated SMAD2 (pSMAD2) levels in a quantitative ELISA and gene expression by Affymetrix microarray and RT-PCR analyses. Confirmatory studies were also carried out in mice treated with two weekly doses of the murine form of STX-100. RNA was also isolated from twenty BAL cell samples from IPF patients to determine inter-patient variability in gene expression (coefficients of variation) for subsequent power calculations.

Results: BAL cells isolated from mice and primates treated with ≥ 1 mg/kg anti-αvβ6 antibody showed significant inhibition of pSMAD2 and TGF-β inducible genes. A dose of 1 mg/kg antibody was previously found to have maximal anti-fibrotic activity in multiple disease models. Power calculations integrating the treatment effect observed at 1 mg/kg antibody treatment and the coefficient of variation measured in IPF BAL cells indicated that pSMAD2 levels and > 250 of the genes should be adequately powered in our Phase 2a trial.

Conclusion: We have identified pharmacodynamic biomarkers of STX-100 mediated inhibition of the TGF-β pathway that can be monitored in BAL cells recovered from IPF patients. The significance of these biomarkers as indicators of potential clinical activity of IPF is supported by observations that the TGF-β pathway is reproducibly upregulated in lung tissue from IPF patients and that TGF-β protein is observed at the site of fibrotic lesions, mirroring the expression of αvβ6 in IPF lung tissue (Horan 2008 et al). These endpoints represent mechanistic biomarkers that can be evaluated in early clinical trials of short duration. Our findings support a role for αvβ6 in fibrotic disease and highlight the potential for therapeutic intervention with STX-100.
Lung Injury and Repair
Leader: Gregory P. Cosgrove, MD

IPF – What’s Age Got to Do With It?
Joseph Lasky, MD

A Stressful Environment Leading to Epithelial Injury
Timothy S. Blackwell, MD

Fibroblasts and Extracellular Matrix: Too Much of a Good Thing?
Eric S. White, MD

Mediators of the Fibroproliferative Injury—Interactions Between the Epithelium and Fibroblast
Andrew M. Tager, MD

Roundtable Discussion
Gregory P. Cosgrove, MD; Timothy S. Blackwell, MD; Joseph Lasky, MD; Eric S. White, MD; Andrew M. Tager, MD; and Glenn D. Rosen, MD

To download presentation slides, please visit
www.ipfsummit.org/slides
Lung Injury and Repair

Notes
Notes
Genetics and Biomarkers

Leaders: Imre Noth, MD and Christine Kim Garcia, MD, PhD
Panel: Naftali Kaminski, MD and David A. Schwartz, MD

Defining the Challenges – What Biomarkers Do We Need?
Imre Noth, MD

The Genetic Basis of IPF
David A. Schwartz, MD

Blood Based Biomarkers to Diagnose and Predict Outcome of IPF
Naftali Kaminski, MD

From Bench to Bedside - An Investigator’s Personal Perspective on Taking a Basic Finding to the Real World of Patient Management
Kenneth B. Adler, PhD

Biomarkers for Disease Activity: Designing Drug Studies and Managing Patients
Fernando J. Martinez, MD, MS

Beyond Rales: Are We Really There Yet?
Christine Kim Garcia, MD, PhD

Roundtable Discussion
Imre Noth, MD; Christine Kim Garcia, MD, PhD; Naftali Kaminski, MD; and Fernando J. Martinez, MD, MS

To download presentation slides, please visit
www.ipfsummit.org/slides
Genetics and Biomarkers

Notes
Notes
Notes
Drug Development in IPF

This session is not accredited for CME

Leaders: A. Bruce Montgomery, MD; Harold R. Collard, MD; and Kevin K. Brown, MD

Session Overview
A. Bruce Montgomery, MD

Drug Development in IPF: Lessons Learned from Phase III Clinical Trials
Kevin K. Brown, MD and A. Bruce Montgomery, MD

Drug Development in IPF: From the Bedside to Approval
A. Bruce Montgomery, MD and Marianne Mann, MD

Roundtable Discussion
Harold R. Collard, MD; Ganesh Raghu, MD; Fernando J. Martinez, MD, MS; Williamson Bradford, MD, PhD; A. Bruce Montgomery, MD; Shelia Violette, PhD; Talmadge E. King, Jr, MD; and Ritu S. Baral

To download presentation slides, please visit
www.ipfsummit.org/slides
Drug Development in IPF

Notes

__________________________________________________________________________

__________________________________________________________________________

__________________________________________________________________________

__________________________________________________________________________

__________________________________________________________________________

__________________________________________________________________________

__________________________________________________________________________

__________________________________________________________________________

__________________________________________________________________________

__________________________________________________________________________

__________________________________________________________________________

__________________________________________________________________________

__________________________________________________________________________

__________________________________________________________________________

__________________________________________________________________________
Clinical Sessions
Leader: Jeffrey J. Swigris, DO, MS

Establishing a Confident Diagnosis
Kevin R. Flaherty, MD, MS

Connective Tissue Fibrotic Disorders
Aryeh Fischer, MD

Pulmonary Hypertension
David A. Zisman, MD, MS

Treatment Options
Kevin K. Brown, MD; Ganesh Raghu, MD; and Marvin I. Schwarz, MD

Case Presentations with Master Clinicians
Kevin K. Brown, MD; Ganesh Raghu, MD; Marvin I. Schwarz, MD; Talmadge E. King, Jr, MD; Aliya N. Husain, MD; and John David Armstrong II, MD, MA

To download presentation slides, please visit
www.ipfsummit.org/slides
Notes
Notes
Notes
Update on Transplantation

Leader: Robert B. Love, MD

Recent Trends and Results
Kenneth R. McCurry, MD

Treatment of Acute Rejections and BOS
Timothy P. Whelan, MD

Ex-Vivo Perfusion
Robert B. Love, MD

Update on ECMO
Charles Hoopes, MD

To download presentation slides, please visit
www.ipfsummit.org/slides
Update on Transplantation

Notes

________________________________________________________________________________
________________________________________________________________________________
________________________________________________________________________________
________________________________________________________________________________
________________________________________________________________________________
________________________________________________________________________________
________________________________________________________________________________
________________________________________________________________________________
________________________________________________________________________________
________________________________________________________________________________