Dear Friends of the Foundation,

Welcome to the PFF Summit 2013: From Bench to Bedside. This is our second biennial scientific healthcare conference. We are once again quite fortunate in being able to assemble an outstanding, international faculty. We 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 idiopathic pulmonary fibrosis (IPF). We are pleased to once again provide sessions for both professionals and patients and caregivers. Education is an important part of our mission, and in order to reach as many people as possible, webinars of all sessions will be available post-Summit.

As many of you know, the Foundation was the brainchild of my father, Albert Rose, and his brother, Mike Rosenzweig, who had IPF. Their sister, Claire, died from the disease and they were both personally driven to help find a cure. My father died in 2002, but his brother continued to work passionately to help find a cure until he passed away in 2012. I am extremely honored to carry on our family legacy as Chief Executive Officer and Chairman of the Board of Directors for the Foundation. Over the past twelve years, the Foundation has become a beacon for those afflicted with this deadly disease. Summit 2011 was highly successful and created many new in-roads for international collaboration, enabling us to provide more information and support to patients, and to help clinicians and researchers around the world make meaningful connections with one another.

Many people have worked hard to organize this year’s Summit. I would like to thank the Foundation’s staff and our partner, National Jewish Health, for what was truly a team effort to make 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 both our individual and corporate sponsors for their generosity.

Since we last gathered for Summit 2011, there has been an increase in interest in drug development for IPF. There are a number of exciting therapies that are in early development while others are working their way through the clinical trial process. It is critically important for patients to participate in clinical trials. This is the only way we can develop new, effective treatments. 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 to all of us, and I assure everyone that we will continue to work tirelessly to help find a cure for IPF.

Warmest Regards,

DANIEL M. ROSE, MD
CHIEF EXECUTIVE OFFICER AND CHAIRMAN OF THE BOARD OF DIRECTORS
PULMONARY FIBROSIS FOUNDATION
Dear Colleagues,

It is a true pleasure to welcome you to the *PFF Summit 2013: From Bench to Bedside*. Despite two decades of progress, our understanding of the pathobiology, and more importantly, our ability to treat pulmonary fibrosis (PF), remains a challenge. In order to address this deficit we held the first *Summit* in 2011 to expand our collective knowledge and encourage the development of new treatment options. This year, physicians, researchers, patients, family members, and industry representatives are gathering together again to learn, collaborate, and share information.

The Pulmonary Fibrosis Foundation and National Jewish Health have organized the *PFF Summit 2013* to provide the most up-to-date material to the medical and research communities and much-needed information and support to those affected by this disease. This innovative conference includes a faculty of distinguished experts in the field of pulmonary fibrosis from around the world who have created an outstanding program. The *Summit* gives us an opportunity to combine our talents and dedication to work towards a single goal: making a difference to those who suffer from PF.

We are honored and excited to be the Program Chairs for the *PFF Summit 2013*, and thank each of you for attending and sharing your experience, knowledge, and expertise. Your engagement and input during the *Summit* will help shape the next decade of pulmonary fibrosis research, and through our collective efforts we can improve the future of those affected by these terrible diseases.

Sincerely,

**GREGORY P. COSGROVE, MD**  
National Jewish Health & University of Colorado Denver

**MARTIN KOLB, MD, PhD**  
McMaster University

**PATRICIA J. SIME, MD**  
University of Rochester Medical Center
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OUR 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, promote disease awareness, and provide a compassionate environment for patients and their families.

CURRENT INITIATIVES

The PFF's strategic plan includes initiatives to:

- Increase funding for PF research through independent foundation grants, and partnership grants with the American Thoracic Society, the American College of Chest Physicians, and the National Institutes of Health.
- Facilitate collaboration between the academic research community and the bio-pharma industry.
- Establish a Pulmonary Fibrosis Foundation Care Center Network and Pulmonary Fibrosis Foundation Patient Registry.
- Foster interaction and innovation among physicians, researchers, allied health professionals, patients, and caregivers at our biennial international conference, *PFF Summit: From Bench to Bedside*.
- Expand our support group network to include the international PF community, assist in the development of local support groups, and improve access to the PFF online support groups.
- Implement new patient education and disease awareness programs utilizing webinars, online support services, and social media platforms.
- Support the needs of our constituents through legislative advocacy.
- Increase disease awareness though education, traditional media, social media, and community events.
HISTORY

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

Daniel M. Rose, MD, the son of Albert Rose and chairman of the Board of Directors, assumed the positions of President and Chief Executive Officer in March 2009 when Dr. Rosenzweig retired due to the progression of his disease. 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 in its second decade.

Dr. Rosenzweig lost his courageous battle against IPF on June 23, 2012. Dr. Rose and the Foundation’s staff are honored to carry on his vision of finding successful treatments and hopefully a cure for pulmonary fibrosis. Learn more about how the PFF is making a difference to the PF community at www.pulmonaryfibrosis.org.
the foundation
about the pulmonary fibrosis foundation

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*Member of the Research Advisory Committee
the foundation
about the pulmonary fibrosis foundation

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*Member of the Research Advisory Committee
One of the primary goals of the Pulmonary Fibrosis Foundation (PFF) is to fund research that will lead to successful therapies for pulmonary fibrosis (PF). As part of this commitment, the Foundation supports new research through grants funded solely by the PFF and through partnership grants with other organizations.

The PFF Research Fund was established with the primary goal of funding innovative grants that offer a high likelihood of advancing research that could translate into successful therapies.

PRIMARY OBJECTIVES

FUND INNOVATIVE AND PROMISING RESEARCH

- **I.M. Rosenzweig Young Investigator Awards**: These awards of up to $50,000, given over a two-year period, encourage young investigators* to maintain and enhance their interest in PF research during the early stages of their academic careers. (*individuals within five years of completion of their formal training*)

- **Albert Rose Established Investigator Awards**: These awards of up to $50,000, given over a two-year period, allow established investigators* to explore innovative areas of research that may not yet be eligible for federal grants. (*individuals who have demonstrated a clear record of successful independent research as defined by publication record and current or previous funding from a major organization*)

- **Special Needs Awards**: These awards, granted periodically as needs arise, provide funds for investigators and institutions to “fill the gaps” of financial need where unique circumstances exist and additional funding will help advance an exceptional research effort.

- **Partnership grants with the American Thoracic Society and the American College of Chest Physicians**: These unique partnerships allow the PFF, in collaboration with leading lung health organizations, to jointly award grants focusing on PF.

PROVIDE DONOR GRANT GUIDANCE AND ADMINISTER DONOR-ADVISED FUNDS

The Foundation provides oversight for a donor wishing to make a restricted gift to a specific institution (or institutions) or support a specific research project. The Foundation receives a small percentage of the total grant to administer the grant and to provide oversight.

FOSTER FUNDING OPPORTUNITIES FOR PF RESEARCH

The Foundation continually seeks ways to increase research funding through partnerships with industry, governmental agencies, and other foundations.

Learn more at www.pulmonaryfibrosis.org/research/PFFgrants.
LET THE WORLD KNOW

SEPTEMBER 2014

www.globalPFawareness.org
save the date!

NOVEMBER 12–14, 2015

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 the PFF Summit 2015, or to be placed on the pre-registration list, please email summit@pulmonaryfibrosis.org or call 888.733.6741 or +1 312.587.9272.
meeting information and procedures

ACCREDITATION AND DESIGNATION STATEMENTS
Accreditation and designation information can be found on page 28.

SIGN-IN SHEET AND EVALUATION FORM FOR CME
Please remember to sign in each day at the Registration Desk in order to receive your CME/CE credit for participating in the conference. At the conclusion of the conference, complete the post-test and the evaluation and return them to the Registration Desk or to any conference staff.

CERTIFICATE OF ATTENDANCE
For your convenience in reporting CME, nursing CE, or CRCE credit, you will receive a certificate via email within 30 days of completion of this activity.

NAME BADGE
Your name badge is your admittance to activities during the conference. 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 the Welcome Reception, Networking Dinner, and meal functions. The Exhibit/Poster Hall is located in the Vicino Ballroom and is open during the following hours:

- Thursday, December 5: 5:00 p.m. – 8:00 p.m.
- Friday, December 6: 7:00 a.m. – 5:45 p.m.
- Saturday, December 7: 6:45 a.m – 3:00 p.m.

Breakfasts, lunches, 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 sessions.

OXYGEN STATION
Oxygen refills will be available during Summit hours on Friday, December 6 and Saturday, December 7 to patients with valid prescriptions and who have made an advanced request.
“TOGETHER WE WILL MAKE A DIFFERENCE IN PF . . . “
MESSAGE BOARD AND COMMUNITY MAP

Connect. Collaborate. Inspire. The Message Board is a place for conference attendees to leave inspirational messages.

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 boards are located near the Registration Desk.

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 PFF SUMMIT 2013

The PFF Summit 2013 will be photographed, videotaped, and/or recorded in its entirety by staff and third party vendors. All sessions will be available post-conference on, but not limited to, the Pulmonary Fibrosis Foundation’s and PFF Summit’s websites. 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 Summits, including but not limited to the websites, 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 an orange name badge lanyard at registration for identification. Recording of any session by attendees is strictly prohibited.

DISCLAIMER

The views of the speakers do not necessarily reflect the views of the presenting, partnering, or endorsing organizations. The Pulmonary Fibrosis Foundation and National Jewish Health 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 and National Jewish Health assume no liability for the information herein.

QUESTIONS OR ASSISTANCE

If you have any questions or need assistance, please visit the Registration/Information Desk.
meeting info and space map(s)
navigating the summit

THURSDAY

1 INFORMATION DESK
GRAND FOYER

2 EXHIBIT HALL
VICINO BALLROOM

3 POSTER HALL
VICINO BALLROOM

A WELCOME RECEPTION AND
POSTER PRESENTATIONS
VICINO BALLROOM
meeting info and space map(s)
navigating the summit

FRIDAY

1 REGISTRATION/INFORMATION DESK
   GRAND FOYER

2 EXHIBIT HALL
   VICINO BALLROOM

3 POSTER HALL
   VICINO BALLROOM

4 PATIENT AND CAREGIVER SESSIONS
   AVENTINE BALLROOM A, B, C

5 PROFESSIONAL SESSIONS
   AVENTINE BALLROOM D, E, F, G

6 PATIENT AND CAREGIVER SESSIONS
   OVERFLOW
   PALATINE

7 PROFESSIONAL SESSIONS OVERFLOW
   PORTOFINO

8 SPEAKER READY (FACULTY AND STAFF ONLY)
   PALMERO

9 OXYGEN REFILLS
   FOYER II

A ONLINE > OFFLINE MEET + GREET
   (PATIENTS AND CAREGIVERS ONLY)
   FOYER II

B NETWORKING DINNER RECEPTION
   ASTERIA TERRACE, FOYERS

C NETWORKING DINNER
   AVENTINE BALLROOM
SATURDAY

1. REGISTRATION/INFORMATION DESK
   GRAND FOYER

2. EXHIBIT HALL
   VICINO BALLROOM

3. POSTER HALL
   VICINO BALLROOM

4. PATIENT AND CAREGIVER SESSIONS
   AVENTINE BALLROOM A, B, C

5. PROFESSIONAL SESSIONS
   AVENTINE BALLROOM D, E, F, G

6. PATIENT AND CAREGIVER SESSIONS OVERFLOW
   PALATINE

7. PROFESSIONAL SESSIONS OVERFLOW
   PORTOFINO

8. SPEAKER READY (FACULTY AND STAFF ONLY)
   PALMERO

9. OXYGEN REFILLS
   FOYER II
## Friday > Scientific Sessions

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<td>Registration and Continental Breakfast</td>
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<tr>
<td>8:00 a.m.–8:15 a.m.</td>
<td>Welcome and Introduction</td>
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<tr>
<td>Daniel M. Rose, MD</td>
<td>CEO and Chairman of the Board, Pulmonary Fibrosis Foundation</td>
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<tr>
<td>8:15 a.m.–8:45 a.m.</td>
<td>Opening Session Keynote Address (Not Certified for CME)</td>
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<tr>
<td>Robert J. Beall, PhD</td>
<td>President and CEO, Cystic Fibrosis Foundation</td>
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<tr>
<td>LUNG INJURY AND REPAIR</td>
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<td>LEADERS: Gregory P. Cosgrove, MD; Martin Kolb, MD, PhD; Patricia J. Sime, MD</td>
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<tr>
<td>8:45 a.m.–9:00 a.m.</td>
<td>Introduction: Lung Injury and Repair</td>
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<tr>
<td>Gregory P. Cosgrove, MD</td>
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<tr>
<td>9:00 a.m.–9:30 a.m.</td>
<td>Targeting Matrix: Opportunities for Therapy</td>
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<td>Patricia J. Sime, MD</td>
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<tr>
<td>9:30 a.m.–10:00 a.m.</td>
<td>Role of Alveolar Epithelium in Pulmonary Fibrosis: Innocent Bystander or Active Participant?</td>
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<td>Zea Borok, MD</td>
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<tr>
<td>10:00 a.m.–10:30 a.m.</td>
<td>Visit Exhibits and View Posters</td>
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<tr>
<td>10:30 a.m.–11:00 a.m.</td>
<td>IPF Fibroblasts and Their Cell-Of-Origin</td>
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<td>Craig Henke, MD</td>
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<td>11:00 a.m.–11:30 a.m.</td>
<td>Cell Based Therapy to Correct the Tissue Milieu in IPF</td>
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<td>David Warburton, MD</td>
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<td>11:30 a.m.–12:00 p.m.</td>
<td>Panel Discussion</td>
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<tr>
<td>LEADER: Martin Kolb, MD, PhD</td>
<td>PANEL: Gregory P. Cosgrove, MD; Patricia J. Sime, MD; Zea Borok, MD; Brigitte Gomperts, MD; Craig Henke, MD</td>
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<td>When Drug Research is Personal: The Importance of Patient Advocacy in Drug Development and Innovation</td>
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<tr>
<td>John F. Crowley, JD, MBA</td>
<td>Chairman and CEO, Amicus Therapeutics</td>
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<tr>
<td>12:45 p.m.–1:00 p.m.</td>
<td>Break</td>
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PERSONALIZED MEDICINE: GENETICS AND BIOMARKERS
LEADER: Fernando J. Martinez, MD, MS

1:00 p.m.–1:05 p.m.  INTRODUCTION: GENETICS AND BIOMARKERS
Fernando J. Martinez, MD, MS

1:05 p.m.–1:30 p.m.  GENETIC MARKERS: IMPACT ON OUTCOME AND PATIENT MANAGEMENT
Christine Kim Garcia, MD, PhD

1:30 p.m.–1:55 p.m.  GENOME-WIDE APPROACH TO A PERSONALIZED SURVIVAL IN IPF
Imre Noth, MD

1:55 p.m.–2:20 p.m.  IMPLEMENTING PROTEIN-BASED BIOMARKERS IN IPF: CHALLENGES AND FUTURE DIRECTIONS
Ivan O. Rosas, MD

2:20 p.m.–2:45 p.m.  VISIT EXHIBITS AND VIEW POSTERS

2:45 p.m.–3:15 p.m.  IMPLICATIONS OF GENETIC TESTING
Janet Talbert, MS, CGC

3:15 p.m.–3:45 p.m.  PANEL DISCUSSION
LEADER: Fernando J. Martinez, MD, MS
PANEL: Christine Kim Garcia, MD, PhD; Imre Noth, MD; Ivan O. Rosas, MD; Janet Talbert, MS, CGC

DRUG DEVELOPMENT IN IPF (NOT CERTIFIED FOR CME)
LEADERS: A. Bruce Montgomery, MD; Dean Sheppard, MD

3:45 p.m.–4:00 p.m.  INTRODUCTION: COMPARISON OF REGULATORY AGENCIES AND THE APPROVAL PROCESS
A. Bruce Montgomery, MD

4:00 p.m.–4:30 p.m.  PROMISING THERAPEUTIC TARGETS
Dean Sheppard, MD

4:30 p.m.–5:00 p.m.  CHALLENGES OF IPF DRUG DEVELOPMENT
Tom O’Riordan, MD

5:00 p.m.–5:30 p.m.  PANEL DISCUSSION
PANEL: A. Bruce Montgomery, MD; Dean Sheppard, MD; Ritu S. Baral; Williamson Bradford, MD, PhD; Alan H. Cohen, MD; Tom O’Riordan, MD; Eugene J. Sullivan, MD; Shelia Violette, PhD

5:30 p.m.–5:45 p.m.  CLOSING REMARKS
Daniel M. Rose, MD
CEO and Chairman of the Board, Pulmonary Fibrosis Foundation

6:30 p.m.–10:00 p.m.  NETWORKING DINNER
saturday > clinical sessions

LEADERS: Kevin R. Flaherty, MD, MS; Marvin I. Schwarz, MD; Jeffrey James Swigris, DO, MS; Leslie C. Watters, MD

6:45 a.m.–7:45 a.m. REGISTRATION AND CONTINENTAL BREAKFAST

7:45 a.m.–8:00 a.m. WELCOME
Daniel M. Rose, MD
CEO and Chairman of the Board, Pulmonary Fibrosis Foundation

8:00 a.m.–9:00 a.m. POSTER ABSTRACT PRESENTATIONS
Jesse Roman, MD; Michael F. Beers, MD

9:00 a.m.–9:15 a.m. SESSION INTRODUCTION
Jeffrey James Swigris, DO, MS

9:15 a.m.–10:00 a.m. MAKING AN ACCURATE DIAGNOSIS: HOW TO USE THE IPF CONSENSUS GUIDELINES
Fernando J. Martinez, MD, MS

10:00 a.m.–10:15 a.m. BREAK

10:15 a.m.–10:45 a.m. SLEEP APNEA AND IPF: COINCIDENCE OR CAUSATION?
David Lederer, MD, MS

10:45 a.m.–11:15 a.m. PULMONARY HYPERTENSION IN PF: TO TEST? TO TREAT?
Steven M. Kawut, MD, MS

11:15 a.m.–11:45 a.m. GERD AND MICROASPIRATION IN PF: FUNDOPICATION FOR EVERYONE?
Joyce Lee, MD

11:45 a.m.–12:00 p.m. QUESTIONS AND ANSWERS
LEADER: Leslie C. Watters, MD
All Clinical Session Faculty

12:00 p.m.–12:15 p.m. BREAK

12:15 p.m.–1:15 p.m. LUNCH SESSION
CASE PRESENTATIONS WITH MASTER CLINICIANS
PANEL: Marvin I. Schwarz, MD; Steve D. Groshong, MD, PhD; Talmadge E. King, Jr., MD; David Lynch, MD; Ganesh Raghu, MD
<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Presenter(s)</th>
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<tr>
<td>1:15 p.m.–1:30 p.m.</td>
<td>BREAK</td>
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<tr>
<td>1:30 p.m.–2:15 p.m.</td>
<td>TALKING WITH PF PATIENTS: TRUTH-TELLING</td>
<td>Jeffrey James Swigris, DO, MS</td>
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<td>EXISTING AND NEW TREATMENT OPTIONS:</td>
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<td>A GLOBAL PERSPECTIVE</td>
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<td>LEADERS: Kevin K. Brown, MD; Christopher J. Ryerson, MD;</td>
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<tr>
<td>2:15 p.m.–2:25 p.m.</td>
<td>NON-PHARMACOLOGIC TREATMENT OPTIONS</td>
<td>Christopher J. Ryerson, MD</td>
</tr>
<tr>
<td>2:25 p.m.–2:35 p.m.</td>
<td>PIRFENIDONE TREATMENT OF IPF IN THE EUROPEAN UNION</td>
<td>Carlo Vancheri, MD</td>
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<tr>
<td>2:35 p.m.–2:45 p.m.</td>
<td>FUTURE OF THERAPIES AND CLINICAL TRIALS</td>
<td>Kevin K. Brown, MD</td>
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<tr>
<td>2:45 p.m.–3:00 p.m.</td>
<td>BREAK</td>
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<tr>
<td>3:00 p.m.–4:15 p.m.</td>
<td>CLINICAL TRIAL UPDATES (NOT CERTIFIED FOR CME)</td>
<td>Brad Maroni, MD, Biogen Idec; Claudio Pasquinelli, MD, PhD; Bristol-Myers Squibb; Gregory Ferguson, PhD, Celgene; Jack Stauffer, MD, FibroGen; Tom O'Riordan, MD, Gilead; Ari Gershman, DO, Genentech; David Wilkes, MD, ImmuneWorks; Jonathan Leff, MD, InterMune; Elizabeth Trehu, MD, Promedior</td>
</tr>
<tr>
<td>4:15 p.m.–4:25 p.m.</td>
<td>QUESTIONS AND ANSWERS (NOT CERTIFIED FOR CME)</td>
<td>LEADER: Kevin K. Brown, MD</td>
</tr>
<tr>
<td>4:25 p.m.–4:40 p.m.</td>
<td>EFFECTIVE ADVOCACY FOR PF</td>
<td>Brian Baird, MS, PhD</td>
</tr>
<tr>
<td>4:40 p.m.–4:45 p.m.</td>
<td>CLOSING REMARKS</td>
<td>Daniel M. Rose, MD</td>
</tr>
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<td></td>
<td></td>
<td>CEO and Chairman of the Board, Pulmonary Fibrosis Foundation</td>
</tr>
</tbody>
</table>
learning objectives

The following educational objectives for this program were developed to address the educational needs identified in the Needs Assessment. Following completion of this educational activity, participants should be able to:

- Differentiate between interstitial lung diseases (ILDs) resulting in pulmonary fibrosis (PF)
- Describe a systematic approach for accurately diagnosing idiopathic interstitial pneumonias (IIPs), including idiopathic pulmonary fibrosis (IPF)
- Explain the pathophysiology of IPF based on most current data
- Discuss recent evidence for treatments in the management of IPF and fibrosing ILDs other than IPF
- Recognize genetic components of IPF
- Provide patient lifestyle management tools which improve functional status for patients with PF
- Develop a comprehensive approach to the management of IPF, which includes both pharmacologic and non-pharmacologic therapies
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 (ACCME) through the joint sponsorship of National Jewish Health and the Pulmonary Fibrosis Foundation. National Jewish Health is accredited by the ACCME to provide continuing medical education for physicians.

DESIGNATION STATEMENT

National Jewish Health designates this live activity for a maximum of 12.25 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

National Jewish Health is a provider approved by the California Board of Registered Nursing, Provider Number CEP 12724. This program is accredited for a total of 18.1 Nursing Contact Hours. Nursing Contact Hours will be prorated for participants based on the number of days attended. Participant attendance throughout an entire day is required to receive contact hours.

We have applied for Continuing Respiratory Care Education (CRCE) credit through the American Association for Respiratory Care, 9425 N. MacArthur Blvd, Suite 100, Irving TX 75063. Approval and credit hours are pending.

*Please note that the Opening Keynote Address, all of the Drug Development in IPF sessions, and the Clinical Trial Updates session are not certified for CME.
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Biogen Idec  
WESTON, MASSACHUSETTS

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LESLIE C. WATTERS, MD*  
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ATLANTA, GEORGIA

*Member of PFF Summit 2013 Program Committee
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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.

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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.
## FACULTY DISCLOSURES

<table>
<thead>
<tr>
<th>KEY</th>
<th>FACULTY NAME</th>
<th>POSITION</th>
<th>DISCLOSURE INFORMATION</th>
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<tr>
<td>A</td>
<td>BRIAN BAIRD, MS, PHD</td>
<td>ADVISORY BOARD</td>
<td>Antioch University</td>
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<td>B</td>
<td>ROBERT J. BEALL, PHD</td>
<td>BOARD OF DIRECTORS</td>
<td>Vertex</td>
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<td>C</td>
<td>MICHAEL F. BEERS, MD</td>
<td>CONSULTANT</td>
<td>Has no significant financial interest to report</td>
</tr>
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<td>E</td>
<td>ZEA BOROK, MD</td>
<td>EMPLOYEE</td>
<td>Has no significant financial interest to report</td>
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<td>F</td>
<td>MOLLY BOURNE, MD</td>
<td>FOUNDER</td>
<td>Hospice by the Bay</td>
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<td>WILLIAMSMON BRADFORD, MD, PHD</td>
<td>INVESTIGATOR</td>
<td>InterMune</td>
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<td>O</td>
<td>KEVIN K. BROWN, MD</td>
<td>OTHER</td>
<td>Actelion, Altitude Pharma, Amgen, Biogen Idec/Stromedix, Boehringer Ingelheim, Celgene, Centocor, FibroGen, Genentech, GeNO, Genoa Pharma, Gilead, MedImmune, Mesoblast, Novartis, Pfizer, Promedior, Sanofi/Genzyme, Vascular Biosciences, Veracyte</td>
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<td>SP</td>
<td>ERROL L. BUSH, MD</td>
<td>SPEAKER</td>
<td>Has no significant financial interest to report</td>
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<td>SH</td>
<td>ALAN H. COHEN, MD</td>
<td>STOCKHOLDER</td>
<td>Boehringer Ingelheim</td>
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<td>HAROLD R. COLLARD, MD</td>
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<td>FibroGen, Gilead, InterMune, Promedior</td>
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<td>GREGORY P. COSGROVE, MD</td>
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## FACULTY DISCLOSURES (continued)

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| **ROBIN R. DETERDING, MD**  | B ATS, chILD Foundation  
|                             | C InterMune  
|                             | E University of Colorado  
|                             | I SomaLogic, Inc.  |
| **SERPIL C. ERZURUM, MD**   | Has no significant financial interest to report  |
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|                             | C FibroGen, Veracyte  
|                             | SP Boehringer Ingelheim, Forest, France Foundation  |
| **CHRISTINE KIM GARCIA, MD** | Has no significant financial interest to report  |
| **BRIGITTE GOMPERTS, MD**   | Has no significant financial interest to report  |
| **STEVE D. GROSHONG, MD, PHD** | Has no significant financial interest to report  |
| **CRAIG HENKE, MD**         | Has no significant financial interest to report  |
| **ERICA L. HERZOG, MD, PHD** | C Boehringer Ingelheim, Sanofi  
|                             | I Galera Therapeutics, MedImmune, Promedior, Sanofi  |
| **SUSAN S. JACOBS, RN, MS** | Has no significant financial interest to report  |
| **STEVEN M. KAWUT, MD, MS** | I Actelion  
|                             | O Genentech  |
| **DOLLY KERVITSKY, RCP, CCRC** | E Pulmonary Fibrosis Foundation  
|                             | A Boehringer Ingelheim  |
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|                             | SP AstraZeneca, Boehringer Ingelheim, InterMune  |
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| **JOYCE LEE, MD**           | Has no significant financial interest to report  |
| **KATHLEEN O. LINDELL, PHD, RN** | Has no significant financial interest to report  |
| **DAVID A. LYNCH, MD**      | C Boehringer Ingelheim, Genentech, Gilead, InterMune, Perceptive Imagine  
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|                             | SP Boehringer Ingelheim, Nycomed  |
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activity information
disclosure information

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E. Cardeas Pharma

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C. ImmuneWorks
G. InterMune
I. Boehringer Ingelheim, Hoffman-La Roche, Stromedix, Sanofi
O. Up to Date
SP. GlaxoSmithKline

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G. InterMune

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CHILD (CHILDREN’S INTERSTITIAL AND DIFFUSE LUNG DISEASE)
NORWICH, OKLAHOMA

Our Mission is to accelerate research to cure all forms of Children’s Interstitial and Diffuse Lung Disease (chILD) and to provide compassionate support, education, and hope to children and families affected by these life-altering diseases. chILD is not a single disease. Instead it is a group of several rare disorders that affect infants and children, and some of the underlying causes may be linked to adult lung disease.

INSPIRE
PRINCETON, NEW JERSEY

Inspire is the patient engagement company. We build and manage online peer-to-peer support communities for more than 400,000 patients and caregivers, and help industry connect to members for the purpose of research. We partner on our communities with more than 100 nonprofit patient advocacy organizations, including the Pulmonary Fibrosis Foundation, Genetic Alliance, Ovarian Cancer National Alliance, and National Psoriasis Foundation. Find out more at http://corp.inspire.com or by contacting us at team@inspire.com.

INTERMUNE
BRISBANE, CALIFORNIA

InterMune is a biotechnology company focused on the research, development and commercialization of innovative therapies in pulmonology and orphan fibrotic diseases. In pulmonology, the company is focused on therapies for the treatment of idiopathic pulmonary fibrosis (IPF), a progressive, irreversible, unpredictable and ultimately fatal lung disease. InterMune’s research programs are focused on the discovery of targeted, small-molecule therapeutics and biomarkers to treat and monitor serious pulmonary and fibrotic diseases. For additional information about InterMune and its R&D pipeline, please visit www.intermune.com.
MAYO CLINIC
ROCHESTER, MINNESOTA

At Mayo Clinic, over 3,800 doctors and scientists and over 58,000 allied health staff work together to care for people from all walks of life, joined by common systems and a philosophy of “the needs of the patient come first.” Mayo Clinic is a nonprofit organization; for more Mayo news visit www.mayoclinic.org/news.

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 is the leading respiratory hospital in the nation, treating patients from all over the country and conducting innovative and groundbreaking research to improve health worldwide.

PATIENTSLIKEME
CAMBRIDGE, MASSACHUSETTS

PatientsLikeMe® (www.patientslikeme.com) is an online patient network that improves lives and a real-time research platform that advances medicine. Patients connect with others who have the same disease or condition and track their own experiences. In the process, they generate data about the real-world nature of disease that help researchers, pharmaceutical companies, providers, and nonprofits develop more effective products and services. PatientsLikeMe is a trusted source for real-world information and has published more than 35 peer-reviewed articles.

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, promote disease awareness, and provide a compassionate environment for patients and their families. The PFF collaborates with physicians, organizations, patients, and caregivers worldwide. For more information visit www.pulmonaryfibrosis.org.
SCLERODERMA FOUNDATION, GREATER SAN DIEGO CHAPTER
SAN DIEGO, CALIFORNIA

Scleroderma is a rare autoimmune disease for which there is no known cause or cure. Symptoms range from extreme fatigue and joint discomfort to life threatening, hardening of skin and various organs. Treatments exist to alleviate certain symptoms, but we strive to find a cure. Our three-fold mission is providing Support, Education and Research for patients and families affected by scleroderma. We offer monthly Support Group meetings, Education Days, walkathons for Research, and more.

UNIVERSITY OF SOUTHERN CALIFORNIA, CENTER FOR ADVANCED LUNG DISEASE
LOS ANGELES, CALIFORNIA

The USC Center for Advanced Lung Disease is dedicated to helping patients to breathe easier, live longer and enjoy a better quality life by providing excellent, innovative and patient-centered care. Our lung experts provide highly specialized evaluations and treatment options for all patients suffering from complex lung diseases, regardless of their transplant status. Referring physicians have rapid access to physicians who offer vast experience in treating the most severe cases of advanced lung disease. Our personalized interdisciplinary approach consists of many specialties, resulting in comprehensive and individualized diagnostic and treatment plans that produce optimal outcomes.
Summit Supporters Attendees

Attendees as of November 16, 2013

Alphabetical by last name

Andrew Ackrill, PhD; Genentech; San Francisco, CA
Kamyar Afshar, DO; University of Southern California; Los Angeles, CA
Joyce Alejo-Stone; FibroGen; San Francisco, CA
Aviva Alovsh, RN; Washington University School of Medicine; Saint Louis, MO
Michael T. Amato; Inspirx; Durham, NC
Kevin J. Anstrom, PhD; Duke Clinical Research Institute; Durham, NC
Jenny Armstrong; Eisenhower Medical Center; Palm Desert, CA
Heather Arnett, PhD; Amgen; Seattle, WA
Shanna Ashley; University of Michigan; Ann Arbor, MI
Deborah Ayssayag, MD; University of California, San Francisco; San Francisco, CA
Neelam Azad, PhD; Hampton University; Hampton, VA
Lisa D. Bacolini; FibroGen; San Francisco, CA
Kameswara Rao Badri, PhD; Savannah State University; Savannah, GA
Ruth Bailey, PharmD; Gilead Sciences; Seattle, WA
Brian Baird, MS, PhD; Antioch University; Edmonds, WA
Masashi Bando, MD, PhD; Jichi Medical University; Tochigi, Japan
Ritu S. Baral; Canaccord Genuity; New York, NY
Rebecca Bascom, MD, MPH; Penn State College of Medicine; Hershey, PA
Joel Bathe; InterMune Canada; Burlington, ON, Canada
Robert J. Beall, PhD; Cystic Fibrosis Foundation; Bethesda, MD
Michael F. Beers, MD; University of Pennsylvania, Perelman School of Medicine; Philadelphia, PA
Amanda Belkin, MPH; National Jewish Health; Denver, CO
Debbie Benitez, RN; University of Southern California, Keck Medical Center; Los Angeles, CA
Helen Bertron; InterMune; Brisbane, CA
Pauline Bianchi; InterMune; San Diego, CA
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academic posters

The goals of the PFF Summit are to enhance the clinical and scientific knowledge of pulmonary fibrosis in the medical, research, and patient communities. The Pulmonary Fibrosis Foundation (PFF) invited academic researchers to submit abstracts of their scientific research for poster presentation at the PFF Summit 2013: From Bench to Bedside.

Subject matter deemed appropriate for poster presentation at the PFF Summit 2013 include original ideas that will help improve the understanding of pulmonary fibrosis in the following areas:

- Basic Research
- Translational Research
- Clinical Research
- Social Science/Quality of Life Research

Academic abstracts will be reviewed by the PFF’s Research Advisory Committee (RAC).

POSTER AWARDS

Poster awards will be granted to the top three presentations:

- First place: $1,500 and travel award
- Second place: $1,000 and travel award
- Third place: $500 and travel award
- Honorable mentions (2): travel awards

DISCLOSURES

All poster presenters were required to disclose any financial relationship with commercial and non-commercial entities, including tobacco entities.
Periostin Regulation of Mesenchymal Cells in Lung Fibrosis

Shanna L. Ashley1, Payal K. Naik2, Carol A. Wilke2 and Bethany B. Moore2

1) Graduate Program in Immunology, 2) Department of Internal Medicine University of Michigan, Medical School, Ann Arbor, MI 48109

SUMMARY

Periostin is a matricellular protein that influences cellular interactions with extracellular matrix (ECM) and can have profound effects on cell function. We and others have shown increased periostin expression in lung tissue of patients with idiopathic pulmonary fibrosis (IPF). High levels of periostin in the plasma at the time of IPF diagnosis predicted disease progression. Similarly, fibroblasts isolated from IPF lungs expressed higher mRNA levels of periostin than did fibroblasts from normal lungs. In murine models of bleomycin-induced fibrosis, periostin-deficient mice are protected from ECM deposition, and loss of periostin by either structural or hematopoietic cells limits development of pulmonary fibrosis. To better understand the role of periostin in pulmonary fibrosis we performed in vitro analysis of lung mesenchymal cells isolated from wild type (WT) mice by sorting fibroblasts and fibrocytes then treating with periostin. Treatment of cells with periostin increased the expression of the anti-apoptotic protein, X-linked inhibitor of apoptosis protein (XIAP) only in fibrocytes but not fibroblasts. These data suggest periostin is preferentially regulating apoptosis in fibrocytes but not fibroblasts. Transforming growth factor beta stimulation of periostin production is more robust in fibrocytes than fibroblasts. Periostin can increase the rate of wound closure as well as collagen 1 expression in cultures that contain mixtures of fibroblasts and fibrocytes. Whether periostin differentially influences these outcomes in each cell type is currently unknown, but under investigation by us. Periostin interacts with multiple cell surface integrins. The use of a monoclonal antibody to block periostin’s interaction with alpha-V beta 3 and alpha-v-beta 5 integrins partially blocks the effects of periostin on wound closure and bleomycin-induced fibrosis. We have evidence to suggest that there is decreased expression of integrins in fibrocytes from periostin knockout mice treated with bleomycin when compared to wild type mice. Taken together these data suggest that periostin is preferentially regulating apoptosis in fibrocytes but not fibroblasts. In addition the expression of integrins in fibrocytes may contribute to increase periostin in bleomycin-induced fibrosis. Current studies are underway to determine the role of fibrocyte-derived periostin in promoting lung fibrosis.
Endothelial Specific Inhibition of Hypoxia-Inducible Factor Blocks Development of Pulmonary Hypertension Associated with Lung Fibrosis


Division of Allergy, Pulmonary and Critical Care Medicine, and Division of Nephrology & Hypertension, Vanderbilt University School of Medicine, Nashville, TN

Funding: HL85317, HL85406, HL92870, HL105479, HL87738 and ATS PHA

SUMMARY

INTRODUCTION: Although the mechanisms regulating development of pulmonary hypertension in IPF patients are unknown, this complication limits exercise capacity, reduces quality of life, and is associated with increased mortality. Signaling via hypoxia-inducible factor (HIF) has previously been shown to influence the development of hypoxia-induced pulmonary hypertension, leading us to postulate that HIF signaling could be a common mechanism of secondary pulmonary hypertension.

METHODS: Transgenic mice (C57BL/6J background) with endothelial cell specific deletion of HIF1a and HIF2a were generated by crossing mice expressing Cre recombinase under control of the VE-Cadherin promoter with mice genetically engineered to contain loxP sites flanking both HIF1a and HIF2a. Lung fibrosis was then induced by repetitive intraperitoneal dosing of bleomycin (0.035U/g body weight) twice weekly for four weeks. At harvest, right ventricular systolic pressure (RVSP) was measured using a catheter introduced through the right internal jugular vein. Lungs were harvested for histologic evaluation and collagen content and hearts were collected for determination of RV remodeling by the RV:LV+S measurement.

RESULTS: Mice with endothelial cell specific deletion of HIF1a and HIF2a were healthy and lungs had a normal histological appearance. Following bleomycin, lung fibrosis and collagen content were similar between endothelial HIF1/HIF2 deficient mice and wild type controls. However, bleomycin-induced increase in RVSP was completely eliminated in mice with endothelial HIF deficiency, as was RV remodeling. As assessed by muscularized pulmonary vessel count, bleomycin-exposed wild type mice had increased vascular remodeling compared to endothelial HIF deficient mice.
CONCLUSIONS: Attenuation of HIF signaling in endothelial cells blocks development of pulmonary hypertension and protects against RV remodeling upon exposure to chronic hypoxia and in bleomycin-induced lung fibrosis. Thus, HIF signaling in endothelial cells may be a common mechanism of secondary pulmonary hypertension and could represent a new therapeutic target to improve outcomes in IPF.

FIGURE 1. HIF deficient mice are protected against development of pulmonary hypertension and RV remodeling upon exposure to bleomycin.

FIGURE 2. Lung fibrosis and collagen content are similar in HIF deficient mice and controls upon exposure to bleomycin.
Mesenchymal Stem Cell- and Fibroblast-derived Extracellular Vesicles Modify the Phenotype of Recipient Cells in Lung Fibrosis

Cernelc-Kohan M, Wong S, Espinoza C, Taype de Roberts C, Hagood J

SUMMARY

INTRODUCTION: Idiopathic pulmonary fibrosis is a disease of altered mesenchymal-epithelial interactions. In response to stress lung fibroblasts shed extracellular vesicles (EV). EV are submicron, membrane-enclosed vesicles that can be released from mesenchymal stem cells (MSC) as well. EV are increasingly appreciated as critical in cell-to-cell communication. In this study we aimed to determine the role of EV in phenotypic alteration of recipient lung cells.

METHODS: EV were isolated from conditioned media of human mesenchymal stem cells (hmEV) and rat lung fibroblasts (rfEV) at baseline and after stimulation with rhIL-1ß and TNF-alpha. We used sorted Thy-1(+) and Thy-1(-) fibroblasts because we have previously demonstrated their homeostatic and profibrotic phenotypes, respectively. Quiescent MSCs were incubated with Thy-1(+) or Thy-1(-) rfEV. Thy-1(+) or Thy-1(-) rat lung fibroblasts were co-cultured with hmEV. RNA was isolated from recipient cells. We performed RT-PCR on c-DNA reverse transcribed from total RNA using species-specific primers. In human MSC we tested for expression of alpha-SMA, collagen-1 (col1), TGF-ß and fibronectin (FN). In rat lung fibroblasts we analyzed expression of alpha-SMA, col1, plasminogen activator inhibitor-1 (PAI-1) and FN.

RESULTS: EV from either Thy-1(+) or Thy-1(-) fibroblasts stimulated increased expression of coll and FN in human MSC, with a more pronounced effect of EV derived from cytokine-stimulated fibroblasts. HmEV inhibited expression of alpha-SMA, col1 and FN in rat lung fibroblast, whereas they had little effect on expression of PAI-1. Pretreatment of hmEV or rfEV with RNase had no effect on transcriptional effects.

CONCLUSIONS: EV from fibroblasts promote fibroblastic differentiation of MSC in vivo. MSC-derived EV can suppress myofibroblastic differentiation in normal as well as profibrotic fibroblasts. Preincubation of EV did not abolish in vitro effect of vesicles on target cell gene expression, suggesting either that the small RNAs in EV are protected from RNAse or the effects are not mediated by RNA.
Real World Experiences: Pirfenidone is Well Tolerated and Reduces Decline in FVC and DLCO at Nine Months in Idiopathic Pulmonary Fibrosis

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SUMMARY

INTRODUCTION: Idiopathic pulmonary fibrosis (IPF) is a debilitating condition with life expectancy of two to five years from diagnosis. Treatment strategies for IPF are disappointingly limited and pirfenidone is currently the only licensed drug in Europe that has been shown to reduce the decline in forced vital capacity (FVC) at six months. Its use however is compounded by a high adverse effect rate of 98% and 15% drop out rate1.

METHODS: We demonstrate our experience in prescribing pirfenidone in a single centre observational study of forty patients in the United Kingdom involved in a named patient programme (NPP) from September 2011 to January 2013.

RESULTS: We demonstrate that improved adherence and compliance can be achieved by specialist nurse and clinician review, support and education of the patient. Twenty three of 40 (58%) patients experienced more than one adverse effect compared to 98% in clinical trials. The majority of adverse effects were gastrointestinal in nature (87%). Of these adverse effects nine (39%) were self-limiting and resolved with simple measures. Three (13%) resolved after a reduction in dosage, in three (13%) patients pirfenidone was restarted after the adverse effect settled, two (9%) patients died due to their exacerbation. During the first six months of recruitment six (15%) patients discontinued treatment due to adverse effects. In the later ten months we had no discontinuations and this has been attributed to improved education of patients and specialist nursing and clinician review at regular intervals. At nine months before and after pirfenidone commencement we observed a reduction in the decline of mean percentage change of FVC and DLCO with a difference in gradient of -1.043±1.605 vs. -0.197±0.231 for FVC decline and -1.427±1.568 vs. 0.1±0.367 for DLCO decline (Figure 1).
CONCLUSION: In comparison to clinical trials we had fewer adverse effects in our patient group. We believe improved adherence and compliance can be achieved by specialist nurse and clinician review, support and education of the patient. Although our numbers are small we demonstrate a reduction in the decline of FVC and DLCO at nine months, further supporting the role of pirfenidone in the management of IPF.
Asbestosis is Augmented in OGG1 KO Mice by Decreasing Mt-Aconitase and Increasing AEC mt-DNA Damage and Apoptosis

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SUMMARY

RATIONALE: Asbestos causes asbestosis and malignancies by unknown mechanisms. Alveolar epithelial cell injury and repair processes underlie the fibrogenic potential of asbestos. We have previously shown that mitochondrial reactive oxygen species mediate asbestos-induced AEC mitochondrially regulated apoptosis, and that mitochondrial human 8-oxoguanine-DNA–glycosylase 1 prevents oxidant-induced AEC mitochondrial aconitase reductions, mitochondrial DNA damage and apoptosis. We recently reported that ogg1⁻/⁻ mice are more susceptible to fibrotic lung injury than wild-type mice following exposure to crocidolite asbestos.

OBJECTIVE: We wished to determine whether the absence of OGG1 augments murine asbestosis by increasing AEC mtDNA damage and apoptosis.

METHODS: One hundred micrograms of crocidolite asbestos or titanium dioxide suspended in 50µl phosphate buffered saline, PBS alone was instilled intratracheally in male 8-10 week-old C57Bl/6 mice or OGG1 homozygous knockout (ogg1⁻/⁻) mice. Lungs were harvested 21 days later. Collagen was acid-extracted from one lung for collagen determination, while the other was saved for tissue histology, fibrosis score, and Cleaved Caspase 3 (CC-3)/pro-Surfactant protein C (pro-SpC) co-immunostaining. Quantitative PCR-based measurements of mitochondrial and nuclear DNA damage and apoptosis were assessed in primary AT2 cells from ogg1⁻/⁻ mice at baseline as well as 21 d following exposure to crocidolite or TiO2.
RESULTS: Crocidolite exposed ogg1-/- mice exhibit increased pulmonary fibrosis and AEC apoptosis in comparison to WT mice as measured by tissue histology, fibrosis score, lung collagen and AEC apoptosis via CC-3 immunostaining. Further, AT2 cells isolated from ogg1-/- mice had decreased Aco2 levels and increased mtDNA damage and apoptosis. CC-3/pro-SpC co-localization studies are ongoing.

CONCLUSIONS: Compared to WT, ogg1-/- mice have increased pulmonary fibrosis, AT2 cell mtDNA damage and intrinsic apoptosis following exposure to crocidolite asbestos. Given the important role of AEC in pulmonary fibrosis and our recent work suggesting a novel role of Ogg1 and Aco2 in blocking oxidative stress-induced mtDNA damage and apoptosis may be a novel therapeutic target to prevent pulmonary fibrosis.

Matrix Metalloproteinase-8 (MMP-8) Expression is Increased in Idiopathic Pulmonary Fibrosis (IPF) in Lung Macrophages and Epithelial Cells

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SUMMARY

OBJECTIVES: MMP-8 promotes bleomycin-mediated lung fibrosis in mice. Both bone marrow derived cells and lung parenchymal cells are sources of pro-fibrotic Mmp-8. We therefore investigated whether MMP-8 expression and activity was dysregulated in lung and blood specimens from IPF patients compared with controls.

METHODS: MMP-8 protein and steady-state mRNA levels were measured in bronchoalveolar lavage fluid (BALF), lung homogenates, and peripheral blood samples from IPF patients and controls. In order to investigate which cells were sources of MMP-8 we double immunostained IPF and control lung sections.

RESULTS: MMP-8 protein levels are increased ~7 fold (2346 vs. 341 pg/ml, p=0.015) in BALF from patients with IPF compared with healthy volunteers. Western blot shows both active and processed forms of MMP-8 are increased in BALF from IPF patients compared with controls. MMP-8 protein levels are also increased ~22 fold (44.87 vs. 2.09 pg/ml per unit GAPDH,
p = 0.008) in lung homogenates from IPF patients compared with controls (rejected transplant donor lung). Immunostained IPF lung sections show that lung macrophages and airway epithelial cells express increased MMP-8 compared with controls. In peripheral blood plasma MMP-8 protein levels are increased 3.5 fold (1835 vs. 528 pg/ml, p < 0.001) in IPF patients compared with controls. Peripheral blood PMN expressed similar levels of MMP-8 protein and steady-state mRNA, but peripheral blood monocytes from IPF patients expressed increased MMP-8 steady-state mRNA compared with controls (17.04 vs 28.31 delta CT relative to beta actin, p = 0.045).

**CONCLUSIONS:** MMP-8 expression and activity is increased in both lung and peripheral blood compartments in IPF patients. We show for the first time that lung macrophages, epithelial cells, and peripheral blood monocytes have increased expression of MMP-8 in IPF patients compared with controls. Inhibition of MMP-8 in monocytes/macrophages and lung epithelial cells may be beneficial to IPF patients.

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**Epigenetic Repression of Autophagy Machinery in Idiopathic Pulmonary Fibrosis**

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**SUMMARY**

**OBJECTIVES:** IPF is characterized by excessive accumulation of extracellular matrix (ECM). Increased ECM accumulation and failure of ECM turnover is one of the main causes of lung fibrosis. In the normal lung, ECM turnover is controlled by autophagy, an intracellular self-degradation process for turnover of subcellular components. It has been reported that in IPF, autophagy is not induced despite being activated. It is unknown how autophagy dysregulation can influence IPF disease progression. Report that utilized an IPF animal model, treated with rapamycin, a target of rapamycin complex (TorC) inhibitor, did not result in the inhibition of fibrotic genes, but instead activated autophagy machinery in IPF. We hypothesize that autophagy genes are hypermethylated and therefore silenced in patients with IPF, resulting in the inhibition of autophagy machinery to induce cellular senescence.
METHODS: DNA methylation patterns of autophagy genes were determined in human pulmonary fibroblasts, lung tissue from human IPF patients, and lung tissue from bleomycin-treated mice with or without a methylation inhibitor 5’-aza-2’-deoxycytidine (5’aza), treatment. We also examined the expression of DNA methyltransferases (DNMTs), fibrotic genes, and autophagy genes by qRT-PCR and immunoblot in the same samples.

RESULTS: We determined that CpG islands in the promoters of most autophagy genes (Beclin1, Atg5, Atg6, and LC3) were hypermethylated in IPF lung samples compared to control samples. 5’aza treatment relieved the hypermethylation of these genes, allowed for re-expression and attenuated pulmonary fibrosis. A combination of rapamycin and 5’aza demethylated specific autophagy gene promoters to enhance the autophagy cascade and concomitantly decrease fibrotic gene expression.

CONCLUSION: In this study, we propose a novel epigenetic mechanism responsible for augmenting the autophagy pathway in IPF. We demonstrate that repression of autophagy-related genes by hypermethylation is sufficient to inhibit autophagy and decrease cellular senescence in IPF pulmonary fibroblasts. A combination of rapamycin and 5’aza reactivated autophagy machinery and restored gene expression, in vitro. Current studies are underway to evaluate whether this combination attenuates pulmonary fibrosis, in vivo. These studies suggest that 5’aza and rapamycin treatment could be a potential therapy for IPF leading to the hypomethylation of autophagy genes and a decrease in ECM accumulation in the lungs of IPF patients.

ACKNOWLEDGMENTS: supported by NIH/NHLBI/R01 HL102464.
Targeted Depletion of Type II Alveolar Epithelia Provides a Dynamic Functional Model for Chronic Respiratory Disease


*Co-First Authorship

**SUMMARY**

**OBJECTIVES:** Lung Type II alveolar epithelial cells (AEC2) express surfactant protein (SP) and are regarded as a progenitor population for the alveolus, responsible for homeostatic maintenance and injury repair. Loss of AEC2 occurs during both lung disease and injury. An experimental model for targeted AEC2 depletion would provide a platform for understanding alveolar lung injury and repair mechanisms.

**HYPOTHESIS:** Administration of Ganciclovir (GCV) to a transgenic mouse model (termed SPCTK) that expresses thymidine kinase (TKsr39) under control of the SP-C promoter exclusively in AEC2 will cause AEC2 depletion and produce functional outcomes that model lung disease.

**METHODS:** GCV was administered at 10, 25 and 50mg/kg doses via intraperitoneal injection for 3 days to cause varying levels of AEC2 depletion. Experimental and control cohorts were sacrificed at 28 and 60 days following the last GCV injection to determine the specificity of AEC2 depletion and regeneration and the long-term impact of these processes.

**RESULTS:** Characterization of the SPCTK construct demonstrated specificity and dose-dependent sensitivity to GCV in vitro and in vivo. In vivo, AEC2 depletion resulted in long-term functional changes in lung mechanics, changes in lung cell protein expression and changes in lung cytokines that depended on the initial GCV dose. The 10mg/kg dose produced an increase in compliance consistent with development of emphysema, while in stark contrast, animals that received a 25 or 50 mg/kg dose demonstrated a decrease in lung compliance consistent with development of fibrosis. Functional changes in all cohorts persisted out to 60 days past the initial AEC2 depletion.

**CONCLUSIONS:** The SPCTK murine model provides for reproducible, targeted, specific and dose dependent depletion of AEC2 with a subsequent, specific chronic change in pulmonary structure and compliance. We propose that this model is a novel, flexible and useful tool for the study of chronic lung injury and remodeling.
Preclinical Development of Small Molecule Integrin Antagonists for Treatment of Pulmonary Fibrosis

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SUMMARY

OBJECTIVES: All five members of the alpha V integrin family can activate TGFβ, a cytokine that strongly drives organ fibrosis. This functional redundancy, differential expression on epithelial cells and myofibroblasts, and the fibrosis phenotypes of integrin knockout mice [1] all suggest a potent antagonist of this integrin subset is desirable for therapeutic development. Our objectives were to design and optimize such compounds, characterize their drug-like properties, and demonstrate efficacy in diverse animal models of organ fibrosis.

METHODS: Novel stable peptidomimetics of the integrin-binding amino acid sequence RGD were assessed in a comprehensive panel of in vitro integrin function assays. Active and inactive enantiomers of a test compound were administered by continuous infusion at 100 mg/kg/day in mice in which fibrosis was induced in lung by intratracheal bleomycin administration, or in liver by CCl4 injections, or in pancreas by caeruelin injections. Efficacy for lung fibrosis was also assessed with localized daily drug delivery using a microsprayer device from day 14-28 relative to injury. Fibrosis was evaluated by collagen measurement.

RESULTS: Over 25 novel compounds were identified with high potency (IC50 < 10 nM) against all known TGFβ-activating and angiogenic integrins, while sparing the activity of non-targeted integrins. Systemic delivery of a test compound showed significant reduction of fibrosis in all three organ injury models: lung, liver, and pancreas. Direct pulmonary delivery of a single dose of compound suppressed TGFβ signaling for at least 12 hours, and daily pulmonary delivery effectively blocked bleomycin-induced fibrosis (Fig 1). Structural modifications in the compound series improved potency against specific integrins, plasma half-life, and aqueous solubility.

CONCLUSIONS: Efficacy demonstrated in several diverse models of organ fibrosis, including studies with both systemic and localized delivery to mouse lungs, support continued development of multi-functional integrin agents for pulmonary fibrosis treatment.
FIG 1. Daily pulmonary administration of CWHM-12, but not its inactive control enantiomer (CWHM-96), inhibits bleomycin-induced lung fibrosis.


Innate DNA Sensing in Normal and IPF Primary Human Lung Fibroblasts

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SUMMARY

OBJECTIVE: Idiopathic pulmonary fibrosis (IPF) is characterized by the persistence of activated myofibroblasts, excessive deposition of extracellular matrix proteins, and lethal lung remodeling. We have previously reported that primary lung fibroblasts from patients who exhibited rapid progression differentiated into myofibroblasts after exposure to synthetic hypomethylated CpG DNA (CpG) suggesting that innate DNA sensing signaling contributes to the progression of fibrosis in IPF.

METHODS: Using immunofluorescence staining and a variety of pharmacologic inhibitors the role of various DNA sensors in the differentiation of fibroblasts to myofibroblasts was determined.
RESULTS: Consistent with our previous observation that endosomic TLR9 is elevated in rapid IPF, subsequent imaging studies revealed that CpG localized to endosomes in rapid IPF fibroblasts, however we also observed that CpG was present in the nucleus of these cells. Further, pharmacologic inhibition of TLR9 or MyD88 (an adaptor protein involved in TLR signaling) only partially inhibited CpG-induced myofibroblast differentiation, suggesting that primary human fibroblasts expressed other innate DNA sensors. Immunohistochemical staining of IPF lungs indicated that cytosolic LRRFIP1 was strongly expressed in many other cell types other than fibroblasts/myofibroblasts. Interestingly, this DNA sensor was strongly expressed in normal lung fibroblasts. Finally, IPF fibroblasts strongly expressed DNA-protein kinases (DNA-PK; a cytosolic/nuclear DNA sensor) and selective inhibition DNA-PK significantly inhibited the myofibroblast-inducing effects of CpG compared with appropriate control conditions.

CONCLUSIONS: These studies suggest that human fibroblasts express various innate DNA sensors whose activation promote myofibroblast differentiation and the progression of IPF.


Maintaining Compliance of Cryopreserved Lung Bioscaffolds

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SUMMARY

OBJECTIVES: Transplantation is the only viable option for end-stage lung disease. Establishing a cryopreservation protocol for decellularized lung bioscaffolds is vital to increasing the availability of transplantable lungs, which does not satisfy current demand. Decellularized donor lungs can be reseeded with autologous stem cells to eliminate the possibility of immunorejection, thereby creating a clinical biofarm of lung bioscaffolds for transplantation. Our research team has devised a cryopreservation method for lung bioscaffolds using a porcine model as a bridge-to-transplantation.

METHODS: Previously established methods were used to fully decellularize the lungs (n=5) without impacting functionality. Freshly decellularized bioscaffolds were subjected to our cryopreservation technique and later thawed for testing. Lung mechanics were tested before and after decellularization and cryopreservation using a clinical grade ventilator.
RESULTS: Decellularized lung bioscaffold functionality was not altered by cryopreservation. Cryopreserved bioscaffolds showed viable lung compliance (p<.0001), indicating the potential for physiological functionality. Lung mechanical testing showed that lung bioscaffolds were physiologically equivalent before and after cryopreservation. In addition, lung mechanics of bioscaffolds were similar to that of a natural lung.

CONCLUSION: The results indicate that decellularized lungs can be cryopreserved without compromising the physiological functionality. Our developed method is an effective, clinically applicable option for cryopreserving bioscaffolds. Establishing optimal cryopreservation parameters will allow for increased availability of human lungs for transplantation.


A 2 Hit Model of Lung Injury: Prior Insult Alters the Response to Future Injury

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SUMMARY

INTRODUCTION: Recent research into cellular behavior and epigenetic modulation suggest that altered cellular environments can permanently reprogram a cell’s behavior. We used a ‘2 hit’ lung injury model to determine if acute distal lung injury fully resolves, or if it alters the lungs response to subsequent injuries in later life.

METHODS: Using our alveolar epithelial cell type II (AEC2)-specific SPCTK injury model, administration of 50mg/kg ganciclovir (GCV) at 2 months of age caused dose-dependent AEC2 injury in SPCTK mice. 2 or 7 months after this initial injury, a second mild “hit” (10mg/kg GCV) was given. Animals were sacrificed 30 days after the final dose and assayed via pulmonary function testing and sirius red, H&E and fluorescent immunohistochemistry staining.

RESULTS: Following 2 and 7 months of recovery, 2 hit SPCTK mice had reduced lung capacity versus 1 hit mice (19% and 13% respectively) and displayed Pressure-Volume loops shifted downward along the volume axis indicating reduced function and increased stiffening of the lung. 2 hit SPCTK mice exhibited increased hypercellularity and collagen deposition within the
alveolar septa in both recovery cohorts. Collagenous and fibrotic lesions were apparent following 2 months recovery while mice allowed 7 months of recovery displayed less collagen and contained foci of hyperproliferative epithelial cells masses. Following a single dose of GCV, AEC2 numbers in SPCTK mice are maximally decreased after 7 to 14 days before returning to normal levels by 28-60 days. Intriguingly, in 2 hit SPCTK mice AEC2 abundance is substantially increased at 30 days post-treatment versus 1 hit mice, with high numbers of SPC-positive AEC2s present in both the fibrotic regions and hyper proliferative masses of the 2 and 7 month recovery cohorts respectively.

CONCLUSIONS: These results demonstrate that sequential lung injuries cause a more robust response than a single larger event, and drive a more pronounced fibrotic injury. We believe this model better replicates the onset of human fibrosis where multiple insults occur throughout an individual’s lifetime. Furthermore, this work suggests that each insult ‘primes’ the lung to respond differently to later injuries. Ongoing work seeks to identify the cellular changes that control this priming.

Classification of UIP Pattern on CT Using a Novel Combination of Image Texture Descriptors

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SUMMARY

OBJECTIVES: Computed tomography (CT) plays a key role in the diagnosis of idiopathic pulmonary fibrosis (IPF) but identification of a usual interstitial pneumonia (UIP) pattern can be subject to high inter-observer variation. Our objective is to explore quantitative methods, including image texture metrics and machine learning algorithms, to discriminate the characteristic features of a UIP pattern.

METHODS: Fifty five chest CT studies drawn from the IPF Net ACE study [1] were reviewed by two experienced radiologists. Imaging studies were chosen in an effort to maintain consistency in acquisition and reconstruction parameters across the series, but there was a mix of scanner manufacturer and models. Regions of interest (ROIs) demonstrating the key features of a UIP pattern were labeled using an in-house developed software application. Category labels included normal
lung, bronchovascular structures, reticular abnormality, traction bronchiectasis with reticular abnormality, honeycombing, traction bronchiectasis with honeycombing, traction bronchiectasis, and ground glass. Discrete points of interest (POIs) were sampled from within each labeled ROI. A novel image feature descriptor, consisting of multiple local pixel histograms within annular ring shaped regions surrounding each POI, were computed. Outer diameter of these ring shaped regions, reminiscent of a bulls-eye pattern, ranged from 10.0 - 50.0mm and histograms were computed for both pixel intensity and gradient magnitude. These features were used to train a Random Forest (RF) classifier. Testing consisted of leave-one-out cross validation on a case by case basis. In other words, POIs drawn from one chest CT study were held out for testing and data from the remaining 54 cases used for training. The process was repeated over all cases.

RESULTS: Roughly 11,500 POIs sampled from ROIs labeled as fibrotic lung and 3200 POIs from non-fibrotic lung were tested. Leave-one-out cross validation results showed the RF classifier distinguished fibrotic lung with 97.4% accuracy (98.4% sensitivity, 93.7% specificity). Reticular abnormality and honeycombing were classified with 94.1% and 81.7% accuracy respectively.

CONCLUSIONS: These results are promising and support the hypothesis that quantitative methods may provide more precise and specific means for identification of a UIP pattern for diagnosis of IPF.

ACKNOWLEDGMENTS: This work was supported in part by the Colorado Bioscience Discovery Evaluation Grant Program (10BGF-21) and the National Heart, Lung and Blood Institute (IPF Network).

TABLE 1. RF Classifier Results

<table>
<thead>
<tr>
<th>Classifier prediction</th>
<th>ROI Label</th>
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Progressive Allograft Dysfunction Following Lung Transplantation: First Experience with Pirfenidone

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SUMMARY

OBJECTIVES: Chronic lung allograft dysfunction (CLAD) is one of the major factors limiting graft function after lung transplantation (LuTx). No effective medical treatment is available but animal experiments with pirfenidone have shown some promise. The aim of this case report was to evaluate pirfenidone in a LuTx recipient with progressive CLAD.

METHODS: Descriptive data analysis was performed prospectively based on lung function testing, functional outcome and quality of life valuation.

RESULTS: Our case is a 56-year-old female LuTx recipient who underwent LuTx in 2009 due to idiopathic pulmonary fibrosis accompanied by pulmonary hypertension. In 2011 the patient was diagnosed with bronchiolitis obliterans syndrome (BOS) stage 1 (A0/B0). As the patient rapidly progressed to BOS stage 2 and a therapy with azithromycine, montelucast and i.v. steroids as well as a fundoplication were unsuccessful we started a pirfenidone treatment in October 2011. Forced Expiratory Volume in 1 Second (FEV1), Forced Vital Capacity (FVC) and Total Lung Capacity (TLC) before the start of pirfenidone were 1.09l (51%pred.), 2.21l (84%pred.) and 4.24l (95%pred.), respectively. Follow-up pulmonary function tests after three months revealed a FEV1 of 1.26l (59%pred.), a FVC of 2.23l (85%pred.) and a TLC of 4.49l (101%pred.) as well as after six months a FEV1 of 1.30l (61%pred.), a FVC of 2.54l (100%pred.) and a TLC of 4.53l (102%pred.), correspondingly. The distance covered in 6 minutes before the treatment was 510m and during therapy after three months 590m and after six months 580m, respectively. According to the Short Form-36 Health Questionnaire the patient was found to have a good quality of life throughout the conduct of the treatment. Laboratory evaluations including monthly renal- and liver function tests, CMV- and infection screening as well as tacrolimus blood levels showed no change during the administration of pirfenidone.

CONCLUSION: The patient continued on an unchanged dose of pirfenidone and remained on BOSstage2, suggesting attenuation of further progression. Although not conclusive, the potential promise of pirfenidone treatment for CLAD may warrant further investigation.
All-case Post-marketing Surveillance (PMS) of Pirfenidone in Japan: Clinical Characteristics, Efficacy and Safety Profile in 1385 Patients with Idiopathic Pulmonary Fibrosis (IPF)

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SUMMARY

BACKGROUND: In 2008, a novel anti-fibrotic agent, pirfenidone (PFD, Pirespa®) was approved for the treatment of IPF in Japan.

AIMS AND OBJECTIVES: After the approval in 2008, the marketing authorisation holder Shionogi & Co., Ltd. conducted a PMS under government requirement to access the clinical characteristics, efficacy and safety profile of PFD in Japanese clinical setting.

METHODS: All patients (pts) who initiated PFD therapy from Dec 2008 to Oct 2009 in Japan were enrolled. All adverse drug reactions were collected. The efficacy was evaluated on the changes in vital capacity (VC) from baseline. All cases who were enrolled were analyzed up to 1 year from the first dose.

RESULTS: 1370 cases were evaluable for safety. Mean age of pts was 69.5 yrs. At baseline (using Japanese severity grade of IPF), 39.9% of pts were diagnosed as grade IV (\(\text{PaO}_2 < 60 \text{ Torr}\) or \(\text{PaO}_2 < 70 \text{ Torr and 6MWT SpO}_2 < 90\%\)). 62.5% of pts continued PFD therapy for 6 months or longer. Incidences of decreased appetite, photosensitivity reaction and nausea were 27.9%, 14.4% and 7.9%, respectively. Among pts treated with PFD for 6 months or longer, the relative change in VC was -4.77% (mean baseline VC was 2.13 L).

CONCLUSIONS: This is the first official PMS for PFD. The therapy with PFD is generally well tolerated for IPF patients including those with severe disease. The control of gastrointestinal symptoms is thought to be of importance in order that therapy could be continued and maximal benefit from PFD could be gained.
The Lactate Dehydrogenase Inhibitor Gossypol Inhibits TGF induced Myofibroblast Differentiation In Vitro and Bleomycin Induced Pulmonary Fibrosis In Vivo

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SUMMARY

OBJECTIVES: We recently reported that lactic acid concentrations and expression of lactate dehydrogenase (LDH) are increased in idiopathic pulmonary fibrosis. We demonstrated that over-expression of LDH via plasmid transfection in fibroblasts activated latent transforming growth factor beta (TGF-beta) and induced myofibroblast differentiation and that inhibition of LDH using siRNA effectively blocked TGF-beta induced myofibroblast differentiation. We now hypothesize that pharmacologic inhibition of LDH using Gossypol will inhibit TGF-beta induced myofibroblast differentiation in vitro and bleomycin induced pulmonary fibrosis in vivo.

METHODS: Primary human lung fibroblasts were treated with 1, 5 or 10 micromolar Gossypol and/or 1 ng/mL of TGF-beta for 72 hours. Cell lysates were harvested and analyzed for markers of myofibroblast differentiation and extra-cellular matrix protein expression. To test the hypothesis in vivo, 1.5 units/kg of bleomycin or PBS control was administered to C57BL6 mice. Mice were concomitantly treated with either PBS alone, 10 micrograms/kg Gossypol or 25 micrograms/kg Gossypol via daily intraperitoneal injection. Mice were weighed daily and sacrificed on day 7. BALF was analyzed for cell count and differential and lung tissue was analyzed for expression of Col1A1 and fibronectin mRNA.

RESULTS: Gossypol inhibited TGF-beta induced expression of alpha smooth muscle actin, calponin and fibronectin in vitro in a dose dependent manner. In vivo, both 10 micrograms/kg and 25 micrograms/kg of Gossypol prevented bleomycin induced weight loss and inhibited bleomycin induced expression of Col1A1. Gossypol also inhibited bleomycin induced fibronectin expression but to a lesser extent than Col1A1. Gossypol did not have a significant impact on cellular infiltrate or cell differential.

CONCLUSION: We previously reported that excess lactic acid and over-expression of LDH may play an important role in the pathogenesis of pulmonary fibrosis. We have now demonstrated that Gossypol, an LDH inhibitor, effectively blocks TGF-beta induced myofibroblast differentiation in vitro and bleomycin induced pro-fibrotic gene expression in vivo. We are currently testing the effects of Gossypol on bleomycin induced pulmonary fibrosis at day 21 and exploring the mechanisms through which LDH inhibition prevents myofibroblast differentiation in vitro and pulmonary fibrosis in vivo.
Activity of Phosphodiesterase 5 Inhibitors in Decreasing Pulmonary Fibrosis

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SUMMARY

OBJECTIVES: Idiopathic pulmonary fibrosis (IPF) remains an intractably fatal disorder, characterized by the progressive accumulation of extracellular matrix (ECM) proteins, driven by TGF-β (1). Effective agents to treat IPF are lacking. PDE5 inhibitors have been studied in advancing IPF for their effects on pulmonary vascular resistance. However, recent data has suggested that certain PDE5 inhibitors (PDE5-I) may also exert effects on TGF-β activation and hence ECM accumulation.

METHODS: Accordingly, we evaluated gene expression in IPF fibroblasts compared to normal lung fibroblasts to determine whether PDE5-I targetable pathways were expressed in IPF. Subsequently, we studied TGF-β driven ECM generation, epithelial mesenchymal transformation (EMT), and caveolin-1 expression in cultured lung cells treated with PDE5-I's.

RESULTS: Gene expression of IPF derived fibroblasts compared to normal human lung fibroblasts indicated up-regulation of numerous transcripts including thrombospondin and thrombospondin receptors engaged in TGF-β activation. Recent data suggest that certain PDE5-I's may suppress TSP related TGF-β activation and hold promise in treating fibrosis. The PDE5-I's tadalafil and vardenafil, but not sildenafil, significantly inhibited TGF-β mediated ECM (fibronectin and collagen) mRNA levels in lung fibroblasts. In addition, PDE5-I inhibited TGF-β driven EMT in epithelial cells and anchorage-independent growth in fibroblasts. Interestingly, the PDE5-I vardenafil exerted no effect on TGF-β signaling via traditional Smad pathways or downstream PAK2/c-Abl mechanisms. However, vardenafil did inhibit TGF-β mediated reductions of Caveolin-1 protein, an activity associated with the amelioration of fibrosis. Testing of the PDE5-I's in a bleomycin treatment model documented preservation of oxygenation, measures of fibrosis and survival.

CONCLUSIONS: Taken together, these data indicate that certain PDE5 inhibitors may exert activity in suppressing fibroproliferation and EMT in cultured lung fibroblasts in vitro. Select PDE5-I's may yet hold promise in treating IPF, by providing activity beyond their well-established vascular effects.
Analyzing and Comparing RNA-Seq Data from Lung Biopsy and Peripheral Blood Mononuclear Cells of an Idiopathic Pulmonary Fibrosis Patient

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SUMMARY

RATIONALE: Microarrays profiling of peripheral blood mononuclear cells (PBMCs) have been applied in the past to recapitulate idiopathic pulmonary fibrosis (IPF) development as a proxy for the molecular perturbations occurring in lungs. However, since PBMCs are the first line of defense against infection and adapt to intruders, it is debatable whether PBMCs gene expression profiling can reflect changes in lungs.

OBJECTIVE: To compare and contrast differentially expressed genes (DEGs) in lungs and PBMCs of the same patient based on functional similarity to systematically enhance biological interpretation derived from RNA-Seq. Methods. Total RNA of lung biopsy and PBMCs isolated from the same patient was subjected to direct sequencing. RNA-seq data of normal lung was downloaded from Sequence Read Archive (http://sra.dnanexus.com) and used as a calibrator for reads comparison. Raw Illumina reads were processed using RNA-seq pipeline developed in house. Functional annotation enrichment analysis were analyzed by DAVID1,2 tools (http://david.abcc.ncifcrf.gov).

RESULTS: Quality scores across all bases suggest the accuracy of base call >99.9%. DEGs were identified from IPF lungs vs. normal lungs (n=586) and IPF PBMCs vs. normal lungs (n=1070) at FDR 0.05. Only 229 DEGs were overlapped. Gene ontology (GO) analyses revealed major biological process (e.g. cell adhesion, response to wounding, inflammatory and defense response); cellular localization (e.g. plasma membrane, extracellular matrix); molecular function (e.g. cation and carbohydrate binding) categories associated with overlapped DEG list, results congruent with previous findings3,4. Notably, lungs- and PBMCs-specific DEGs were also enriched in the same GO terms listed, suggesting the complexity of gene interaction networks contributed to the pathogenesis of IPF. Furthermore, genes involved in “cell motion” biological process were significantly enriched in PBMCs but not in lungs.
CONCLUSIONS: Analyzing RNA-seq data of lungs and PBMCs from the same patient has provided a list comprehensive DEGs involved in pathological processes, suggesting an incomplete overlap of DEGs in these tissues.

ACKNOWLEDGEMENTS: Pulmonary Fibrosis Foundation (IN); RNA-seq and ITM/CTSA Mini-Awards (SFM); PI11/00074 (MAH); PI11/00623 (CF).

REFERENCES:
Clinical Effect on Incidence of Acute Exacerbation and Lung Carcinoma of Pirfenidone in Chronic Interstitial Pneumonia

Takefumi Saito¹, Yoshiya Tsunoda¹, Toru Tanaka¹, Hiroyuki Takoi¹, Yohei Yatagai¹, Shih-Yuan Lin¹, Akimasa Sekine¹, Kenji Hayashihara¹, Minoru Inomata², Yoshinobu Saito², Arata Azuma²
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SUMMARY

OBJECTIVES: Pirfenidone is the first agent reported to improve progression-free survival in patients with idiopathic pulmonary fibrosis (IPF). However, because it is expensive, slow acting, and not approved for severe IPF except in Japan, prevalence of its use and compliance are current issues. Investigation of its beneficial effects other than inhibition of declines in vital capacity (VC) is needed.

METHODS: From January 2009 to July 2013, 80 patients with chronic interstitial pneumonia treated with pirfenidone were reviewed retrospectively at two institutions. We reviewed the incidence of and mortality from acute exacerbation (AE) and lung carcinoma.

RESULTS: Mean observation time was 23.5 ± 14.5 mo. Incidence of AE was 13.8% (11/80) within the full observation period, 2.5% (2/80) within 9 mo, and mortality was 45.5% (5/11). Incidence of lung carcinoma after therapy was 2.5% (2/80) and mortality was 0%.

CONCLUSION: Incidence of AE was 14.3% at 9 mo, 4.8% at 53 wks in a Japanese phase 2, 3 trials of pirfenidone respectively, 15.7% at 12 mo in a phase 2 trial of BIBF1120, and 20.7% at 36 mo. Lung carcinoma was reported to coexist in 7.1-27.3% of patients with IPF². Interim analysis of post-marketing surveillance in Japan found an incidence of 2.6% (8/302). Transforming growth factor-beta and epithelial mesenchymal transition promote tumor progression. Pirfenidone inhibits both so it may suppress carcinogenesis. However, comparing the incidence of carcinoma among our cases with that in previous reports is difficult because of the wide variation in observation periods. Since mortality from AE and lung carcinoma are both high, their prevention is important to improve prognosis of IPF. Effect of pirfenidone on AE and lung carcinoma is the next challenging focus of investigation of its benefit in IPF.

REFERENCES:
Role of Vascular Endothelial Growth Factor in the Pathogenesis of Bleomycin Induced Pulmonary Fibrosis

Elizabeth S. Monillas, Vani Ramesh, Clayton Wright, Yogesh Kulkarni, Vivek Kaushik, Anand Krishnan, V. Iyer, Neelam Azad

SUMMARY

Pulmonary fibrosis (PF) is a generally fatal, progressive lung disease characterized by fibroblast proliferation, augmented deposition of extracellular matrix, and increased angiogenesis. Reports have demonstrated vascular remodeling in PF and suggested that neovascularization enhances fibrosis. However, the role of the central angiogenic regulator, vascular endothelial growth factor (VEGF), is largely unknown in PF. In normal adult human lung, VEGF is expressed abundantly by various cells however, this protein is abnormally regulated in patients with fibrotic diseases including idiopathic myelofibrosis and diffuse lung fibrosis. We investigated the role of VEGF and related angiogenic proteins in bleomycin-induced pulmonary fibrosis. In this study, we used CR1-1490 lung fibroblasts for in vitro experiments and 6-8 weeks old C57BL/6 mice for in vivo experiments. Both in vitro and in vivo data suggested that bleomycin significantly induced VEGF levels and angiogenesis. Additionally, bleomycin treatment increased levels of other angiogenic proteins, such as protein kinase B (Akt), plasminogen activator inhibitor-1 (PAI-1), CXC chemokine receptors (CXCR1/2). Interestingly, bleomycin treatment led to a decrease in NFkB protein levels. VEGF inhibitor (CBOP11) was used to probe the importance of VEGF in the progression of PF. Co-treatment with CBOP11 significantly inhibited bleomycin induced fibrotic effects, indicating that VEGF significantly contributes to the fibroblast proliferative and collagen-inducing effects of bleomycin. Furthermore, CBOP11 significantly downregulated bleomycin induced expression of the aforementioned angiogenic proteins. Overall, our results indicate that VEGF plays a key role in bleomycin induced pulmonary fibrosis and regulation of this protein may aid in the development of more effective therapies for the disease. It is debatable that angiogenesis may either have a deleterious role, as is the case in cancer, or have an anti-fibrogenic role during the development of pulmonary fibrosis.
Advancing Age Reduces PINK1-mediated Mitochondria Quality Control in Alveolar Epithelial Cells and Promotes Lung Fibrosis

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SUMMARY

RATIONALE: Idiopathic Pulmonary Fibrosis (IPF) is a disease of aging, affecting mostly people over 50 years of age. While familial disease has been related to disordered telomerase activity and mutations of surfactant proteins, the effects of advancing age and lung epithelium dysfunction and fibrosis remains unclear.

METHODS: Lung fibrosis and mitochondria function, morphology and dynamics were analyzed in alveolar epithelial cell type II (AECII) of patients with IPF lungs, aging mice, and mice deficient in the mitochondria quality control protein, PTEN-induced putative kinase 1 (PINK1).

RESULTS: In the current studies we report the unexpected finding of an accumulation of enlarged damaged and dysfunctional mitochondria in AECII in both patients with IPF lungs, aging mice, and mice deficient in the mitochondria quality control protein, PTEN-induced putative kinase 1 (PINK1).

CONCLUSION: Our data identify a novel role for PINK1 in maintaining mitochondrial integrity in AECII and provide insights into the age-related pathogenesis of IPF.

ACKNOWLEDGEMENTS: Vascular Medicine Institute, the Institute for Transfusion Medicine, and the Hemophilia Center of Western Pennsylvania.
Transcriptome Analysis Reveals Differential Splicing Events in IPF Lung Tissue

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SUMMARY

OBJECTIVES: Idiopathic pulmonary fibrosis (IPF) is a complex disease in which a multitude of proteins and networks are disrupted. Interrogation of genome-wide transcription through RNA sequencing (RNA-Seq) enables the determination of genes whose differential expression is most significant in IPF, as well as the detection of alternative splicing events which are not easily observed with traditional microarray experiments.

METHODS: Messenger RNA extracted from 8 IPF lung samples and 7 healthy controls was sequenced on an Illumina HiSeq. Analysis of differential expression and exon usage was performed using Bioconductor packages. The gene periostin was selected for validation of alternative splicing by quantitative PCR, and pathway analysis was performed to determine enrichment for differentially expressed and spliced genes.

RESULTS: There were 873 genes differentially expressed in IPF (FDR 5%), and 440 unique genes had significant differential splicing events (FDR 5%). In particular, cassette exon 21 of the gene periostin was significantly more likely to be spliced out in IPF samples (adj pval = 2.06e-09), and this result was confirmed by qPCR (Wilcoxon pval = 3.11e-4). We also found that genes close to SNPs in the discovery set of a recent IPF GWAS were enriched for genes differentially expressed in our data, including genes like mucin5B and desmoplakin which have been previously associated with IPF.

CONCLUSIONS: There is significant differential splicing and expression in IPF lung samples as compared with healthy controls. We found a strong signal of differential cassette exon usage in periostin, an extracellular matrix protein whose increased gene-level expression has been associated with IPF and its clinical progression, but for which differential splicing has not been studied in the context of IPF. Our results suggest that alternative splicing of periostin and other genes may be involved in the pathogenesis of IPF.

Acute Exacerbation of Idiopathic Pulmonary Fibrosis Following Lung Biopsy; A Case Series

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University of Minnesota in the Pulmonary Allergy Critical Care and Sleep Division

SUMMARY

PURPOSE: Idiopathic pulmonary fibrosis (IPF) is a progressive fibrotic lung disease characterized histologically by the presence of usual interstitial pneumonia (UIP). Median survival is 3 to 5 years. Acute exacerbation of IPF (AE-IPF) has been described, where patients present with acute worsening dyspnea and new ground glass opacities on high resolution chest CT scan (HRCT). There is as yet little information about risk factors for AE-IPF.

METHODS: We performed chart review of 7 patients with AE-IPF following diagnostic video assisted thoracoscopic (VATS) surgical lung biopsies. We examined baseline pulmonary function tests (PFT), HRCTs, comorbidities, smoking status and outcomes.

RESULTS: There were 4 men and 3 women (age 47-71 years). All of the biopsies demonstrated UIP pattern on histology. At the time of AE-IPF, they were treated with high dose corticosteroids and broad-spectrum antibiotics; 6/7 underwent bronchoscopy with bronchoalveolar lavage fluid (BALF) cultures, and only one demonstrated growth of Rhizopus. PFTs were available for 5/7 and demonstrated an FVC range from 55-66% predicted; diffusion capacity of CO (DLCO) range from 36-52% predicted. Five patients had a six minute walk test (6MWT), all of whom
exhibited exertional hypoxia. No patients received blood transfusions. Five patients were on supplemental oxygen prior to admission, and 4 patients were noted to be previous smokers. Four patients demonstrated diffuse ground glass opacities on HRCT, consistent with known literature indicating that severity of AE-IPF is associated with a diffuse pattern on HRCT. One patient had unilateral disease on HRCT. Four patients died during their admission. Notably the 3 patients who survived presented later (> 3 weeks) following their biopsies. Lastly, none of the 7 patients had any particular co-morbidity in common.

CONCLUSIONS: Our case series suggests that VATS surgical lung biopsy might be a risk factor for AE-IPF. Hypoxia on a 6MWT also might predict AE-IPF. Interestingly, later presentation (> 3 weeks) after lung biopsy was associated with an improved survival.

CLINICAL IMPLICATIONS: VATS surgical lung biopsy might be a risk factor for AE-IPF.

Chromosome 17q21 Inversion Polymorphism in Patients with Idiopathic Pulmonary Fibrosis

Justin Oldham, MD, Shwu Fan Ma, PhD, Carley Demchuk, BS, Yong Huang, MD, Imre Noth, MD

SUMMARY

BACKGROUND: Idiopathic pulmonary fibrosis (IPF) is a devastating interstitial lung disease with a 3-5 year median survival. Effective treatment remains elusive and lung transplant remains the sole therapy to prolong survival. While the cause of IPF remains unknown, emerging evidence, including our lab’s recently published genome-wide association study (GWAS), supports a genetic component to this complex disease. An IPF susceptibility gene identified in our GWAS, SPPL2C, is located at chromosome 17q21. Also at this locus is a well-described inversion polymorphism, the haplotype of which is commonly referred to as H2. The role that H2 and genes encoded by this inversion play in IPF pathogenesis is unknown.

METHODS: In this investigation, 120 patients from our group’s GWAS were analyzed to determine the presence of an H2 haplotype. Single nucleotide polymorphisms (SNPs) that tag H2 (rs916793, rs2902662, rs17651213) were used to assign H2 status. SPPL2C variant status was also determined based on the presence of the minor allele of rs17690703.
RESULTS: A total of 34 (28.3%) patients in this IPF cohort were found to carry an H2 haplotype, a 40% increase over the general population of European ancestry estimate. Survival did not differ between individuals with and without an H2 haplotype (34.1 vs 32.9 months, p=0.7). When substratifying these two groups based on SPPL2C variant status, those without an H2 haplotype who carried the SPPL2C variant had a significantly decreased mean survival (13.7 months, p=0.01) compared to the other 3 groups.

CONCLUSION: This investigation suggests that an H2 haplotype may be more common among patients with IPF than that of the general population of similar ancestry. The presence of an H2 haplotype in patients with IPF may be protective against SPPL2C, which was associated with a trend towards decreased survival in our GWAS. Further investigation of H2 and SPPL2C in a larger cohort is needed to explore the interaction between these two genomic variants.

Significant Beneficial Effects of Pirfenidone Treatment in the Caveolin-2 Null Mouse Model of Pulmonary Fibrosis

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SUMMARY

RATIONALE: The natural history of human pulmonary fibrosis (PF) cannot be defined and at the time when a patient seeks medical care the disease is already advanced; thus the only solution to study PF response to different therapies is the use of an animal model reflective of the human disease. Toward this intent we used the caveolin-2 null (cav2-/-) mice that have lung alterations suggestive of PF. Cav2, a membrane protein present in all lung cells has diminished expression, which inversely correlates with the fibrogenic characteristics and functions of PF. Here we examined the effect of long time treatment with pirfenidone on the fibrogenic make-up of cav2 -/- mice.

METHODS: Lung expression of collagen and elastin was analyzed by qPCR and Western blotting in lung lysates of cav2-/- mice untreated (U) and treated with 0.5% pirfenidone (T), for 5 months. In U and T mice the amounts of the two proteins, main structural lung parameters (cellularity, MLI) were determined along with the capacity to adapt to effort (swimming test). Lung extracellular matrix composition was assessed by light (Picrosirius Red staining) and electron microscopy surveys. The functional and biochemical data were analyzed by AINOVA using the SPSS software.
RESULTS: The cav2-/- lungs, display hypercellularity and dramatic alterations of air spaces as revealed by an increase (from 66 to > 130 M) in MLI. A timely raise in the amounts of collagen and elastin is the main signature of cav2-/- phenotype, along with a continuous functional deterioration. A 5 months pirfenidone treatment, of cav2-/- mice, significantly reduced the cellularity, MLI, the levels of collagen and elastin, while improving lung function. Anti-fibrotic effects of pirfenidone demonstrated a linear association between groups (U/wt, T/U) and gender (the fibrosis is more prevalent in males, while the females respond better) and these data are statistically significant.

CONCLUSIONS: Altogether, our findings show that pirfenidone treatment significantly improves lung structure and function in cav2-/- model of PF.

Aged Mesenchymal Stem Cells and IPF

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1The Dorothy P. and Richard P. Simmons Center for Interstitial Lung Disease
2Division of Pulmonary, Allergy, and Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA
3McGowan Institute for Regenerative Medicine, Pittsburgh, PA

SUMMARY

Chronic diseases can be defined as a long duration and slow progression disease that develop slowly over time. In the case of the lung, a chronic disease can be defined as limitation on airflow by any pulmonary disease occurring as result of increased airway resistance or decreased elastic recoil; the entities most often associated with chronic lung disease, Chronic Obstructive Pulmonary Disease (COPD) and many of the interstitial lung diseases (ILD). The most common ILD is Idiopathic Pulmonary Fibrosis (IPF) that represents 45% of the ILD patients. Additionally, the incidence and severity of IPF and emphysema lung diseases increases with age but very little is known about how age-related changes affect the mechanisms that underlie disease emergence and progression. Our own work has demonstrated an increase of susceptibility to chronic lung injury in aged mice. Additionally, we have described that bone marrow derived mesenchymal stem cells (B-MSCs) obtained from old mice are deficient on their multi-linage potential and in their capacity to response to soluble factors. Our data supports the overarching and unique hypothesis that defective lung repair in aging is associated with dysfunctional activation, proliferation, and mobilization of B-MSCs. Furthermore, our data supports
that B-MSCs from IPF patients show signs of exhaustion and are unable to provide protection against injury. We are confident that our studies will help to understand the pathogenesis of other age-associated lung diseases and provide insights for the development of novel strategies for tissue repair.

**Hypersensitivity Pneumonitis–Experience of a Single Center (HYPE Study)**

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University of California, San Francisco - Fresno Educational Program

**SUMMARY**

**OBJECTIVES:** Hypersensitivity pneumonitis (HP), also known as extrinsic allergic alveolitis (EAA), is a complex syndrome caused by repeated inhalation of environmental and occupational antigens. “Chronic” HP may become a relentlessly progressive fibrotic lung disorder. Despite its recognition over many years, published studies have analyzed only specific cohorts of patients such as Bird-fancier’s lungs with an apparent paucity of studies on the “collective” cohort of Chronic HP patients. We wish to present our experience with Chronic HP here at the central valley of California (considered as agricultural heartlands of California).

**METHODS:** A retrospective collection of data from current and past patients with a clear-cut diagnosis of Chronic HP from our collective pulmonary practice at CRMC/UCSF Fresno during 2007-2012.

**RESULTS:** 21 patients with chronic HP were identified (Table-1 lists Baseline characteristics). Only two (.09, 95%CI .03-.19) were current smokers. Exposure history is tabulated in Table-2. Follow up PFTs were available for review in 14 of the 21 patients. Average treatment duration in these 14 patients: 129.625 days +/- 54 days. Pre-treatment FVC in the Corticosteroid (CS) group (N=3) was 2.52 ± 1.3 whereas post treatment FVC was 2.51± 1.2 (p= 0.8). Treatment duration for CS group was 74 days +/- 22. Pre treatment FVC in the group that received both CS and Mycophenolate mofetil (MM) (N=11) was 2.11 ± 1.1 and post treatment FVC was notable for 2.51 ± 1.1 (p=0.06). Treatment duration for this group was 156 days with SD of 98. 17/19 had “clinical” (or subjective) improvement in symptoms. 10 patients had pre and post treatment six minute walk test (6MWT). Mean Pre treatment six minute walk distance (6MWD) was 433m and Post treatment mean 6MWD was 519.8m after average treatment duration of 140 +/- 62 days. 6MWD increased by 87 m (p = 0.054).
CONCLUSIONS: Key observations from our cohort of Chronic HP patients include the following: 1. Female predominant disease with most patients sharing more than 1 exposure and non-smokers. 2. Dyspnea and dry cough were most common presenting symptoms. 3. Treatment with CS and MM resulted in subjective and objective improvement in our cohort of patients.

### Table 1: Demographics

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
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<tbody>
<tr>
<td>Age</td>
<td>59 ±14.6</td>
</tr>
<tr>
<td>Gender (M:F)</td>
<td>6:15</td>
</tr>
<tr>
<td>BMI</td>
<td>29.75 ± 6.2</td>
</tr>
<tr>
<td>Current Active Smokers</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>Presenting Complaint – Dyspnea</td>
<td>19 (90%)</td>
</tr>
<tr>
<td>Presenting Complaint - Cough</td>
<td>18 (86%)</td>
</tr>
<tr>
<td>FVC</td>
<td>2.2 ± 1.02</td>
</tr>
<tr>
<td>FEV1</td>
<td>1.86 ± .86</td>
</tr>
<tr>
<td>TLC</td>
<td>3.6 ± 1.3</td>
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<tr>
<td>DLCO</td>
<td>13.87 ± 7.7</td>
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<tr>
<td>Mean 6 minute walk test</td>
<td>489 m ±112m</td>
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### Table 2: Exposures

<table>
<thead>
<tr>
<th>Type of Exposure</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birds</td>
<td>7 (33%)</td>
</tr>
<tr>
<td>Field Workers</td>
<td>3 (14%)</td>
</tr>
<tr>
<td>Birds and Mold</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Swamp Cooler</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Birds and Swamp Cooler</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Birds, Mold and Swamp Cooler</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Industrial dust and paint</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Hay and Mold</td>
<td>1 (5%)</td>
</tr>
</tbody>
</table>
Physiologic Predictors of Long-Term Survival in Idiopathic Pulmonary Fibrosis

Qingtao Zhou¹, MD; Markus Gutsche², MD, PhD; Susan S. Jacobs², RN, MS; Carissa Davis³, BS; Paul Mohabir², MD; Kapil Patel², MD; Joao de Andrade⁴, MD; and Glenn D. Rosen², MD

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SUMMARY

OBJECTIVES: Many clinical, physiologic and radiological variables have been examined as predictors of survival in idiopathic pulmonary fibrosis (IPF). Data on physiologic predictors of long-term mortality are lacking in this fatal disease, and the role of certain markers as clinically meaningful endpoints, including FVC, has remained unclear.

METHODS: We retrospectively evaluated the Stanford and University of Alabama at Birmingham ILD databases to assess the association between clinical and physiologic variables and long-term survival over 5 years in 150 patients with IPF using Cox proportional hazard regression and Kaplan Meier analysis.

RESULTS: The median age was 64 years, the majority of individuals were male (67%) and white non-hispanic (78%). Surgical lung biopsy was done in 76 patients who showed a histopathological pattern of usual interstitial pneumonia (UIP) and there were 28 patients with lung transplantation. Cox (Forward-Wald) regression analyses were performed using all parameters as covariates, including age, sex, ethnicity, BMI, smoking history, histopathological pattern of UIP, pulmonary hypertension, baseline %predFVC, baseline %predDLco, decline in %predFVC at 12 months from baseline, decline in %predDLco at 12 months from baseline, and oxygen desaturation on 6-minute walk test (6MWT) at 12 months from baseline. In the Cox regression model, statistically significant independent predictors for all-cause mortality were reduced baseline %predFVC, decline in FVC at 12 months by >10%, desaturation at baseline and newly developed desaturation within 12 months from baseline (Table 1). Desaturation at baseline was significantly associated with increased mortality (HR = 2.878, p = 0.001), newly developed desaturation on 6MWT within 12 months from baseline was also strongly associated with decreased survival both on Cox regression (HR =3.551, p=0.001) as well as Kaplan-Meier
analysis (p<0.001, Figure 1) indicating new oxygen desaturation on repeat 6MWT as a strong risk factor for death within 5 years.

CONCLUSIONS: Our findings support the role of reduced baseline FVC and desaturation, a >10% decline in FVC in the first year as clinically meaningful endpoints; also newly developed desaturation is a promising clinical predictor of mortality.

REFERENCES:
Treatment of IPF with Inhaled IFN-gamma; Planning for a Clinical Trial

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SUMMARY

OBJECTIVES: In a recent safety study we analyzed the effect of inhaled interferon-gamma (IFN-gamma) on pulmonary function before and after therapy. We found a significant effect on DLCO. We tested the power of our data to predict an endpoint for a controlled clinical trial.

METHODS: Ten patients with IPF received inhaled IFN-gamma 100 µg 3x/week for 80-130 weeks delivered with I-neb (Philips Respironics), using a monitored slow and deep breathing pattern. Deposition of radiolabeled IFN-gamma in the lungs was determined using a gamma camera. Full PFTs were measured 20-50 weeks before Rx and monthly during Rx. Linear mixed models were used to test the PFT change over time. Autoregressive dependence structure (order one) was the best to model the intra-patient correlation over time. 89 observations were used to build models. PFT with significant changes before and after Rx were used as the primary endpoint to define potential placebo-controlled phase 3 studies.

RESULTS: All patients tolerated at least 80 weeks of inhaled IFN-gamma well, with no systemic side effects. Deposition in the lungs averaged 65.4±4.8µg. DLCO steadily declined in the months before inhaled IFN-gamma therapy. After initiation of inhaled IFN-gamma, there was a marked change in slope of the DLCO curve from negative to positive indicating an improvement in this parameter. The change over time in DLCO was significantly different before and after interferon treatment (Figure 1, p-value=0.03).

FIGURE 1.
Changes in TLC, FRC, RV and FVC were not significant. Power calculations were performed for different sample sizes based on 1000 simulation runs for each sample size. For a sample size of 60, a placebo controlled, randomized trial has a 90% power to detect a significant difference in the change rate of DLCO (Figure 2).

**FIGURE 2.**

**CONCLUSIONS:** Inhaled IFN-gamma is safe with no systemic side effects in IPF over many months of therapy. DLCO appears to be a sensitive index of response to inhaled IFN-gamma. As a result of this response, a relatively small sample size for a placebo-controlled trial is possible.

**ACKNOWLEDGEMENTS:** funded in part by Philips Respironics
Early Predictors of Worse Outcome in Patients with Idiopathic Pulmonary Fibrosis

David Perlman, MD, Manesh Bhargava, MD, Hyun Kim, MD, Melinda Bors, RN, BSN, Philipp Gaillard, PhD, Andrew Wey, MS, Rade Tomic, MD

University of Minnesota

SUMMARY

OBJECTIVES: Idiopathic pulmonary fibrosis (IPF) is a progressive fibrotic disorder resulting in restrictive physiology and impaired gas exchange leading to respiratory failure and death. Currently, there is no effective therapy for halting or slowing disease progression. The IPF trajectory is highly variable and difficult to predict. The purpose of this study was to identify which clinical parameters best predict the course of the disease.

METHODS: Between 2008 and 2012, 98 IPF patients were identified from the Interstitial Lung Disease Database at the University of Minnesota. Participants were clinically diagnosed by surgical biopsy or high resolution CT scan of chest (HRCT). Patients were divided in groups based on body mass index (<35), FEV1/FVC ratio (<0.8), and DLCO (<50%). We investigated the impact of body mass index (BMI), FEV1/FVC ratio, FVC, TLC, and DLCO, as measured during initial diagnosis, on patient survival. Additionally, the relationship between FVC and TLC at the time of diagnosis and its effect on survival was also measured. Controlling for age at diagnosis, gender, and smoking status, a Cox proportional hazards regression analysis was utilized to estimate the association between the predictors of interest and survival.

RESULTS: An initial DLCO < 50% was found to be associated with a considerably higher mortality (p=0.0167) (95% CI 0.50 to 0.93). In contrast, an FEV1/FVC ratio <0.8 was not found to have any predictive value for mortality. A BMI>35 and changes in BMI were not correlated with poorer outcomes. Although a decline in FVC was associated with increased mortality, it did not reach statistical significance (p=0.0530) (95% CI 0.76 to 1.00), but may carry clinical meaningfulness.

CONCLUSIONS: In this cohort of patients, the primary predictor of higher mortality was a DLCO <50% upon initial presentation. Other pulmonary function tests and BMI did not differentiate groups with higher mortality. This data has important implications with regards to prognosis and early referral for lung transplant evaluation. Further studies with larger cohort of patients are needed to verify these findings.
Evidence for an Invasive Fibroblast Phenotype in Idiopathic Pulmonary Fibrosis Mediated by the Toll-like Receptor 9

Varvara Kirillov, Jonathan T. Siler, Mahalakshmi Ramadass, Lingying Ge, Geraldine Grant, Stephen Nathan, Gabor Jarai, Glenda Trujillo

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SUMMARY

OBJECTIVES: We have previously classified IPF patients as rapid/slow progressors based on clinical features and expression of the pathogen recognition receptor, Toll-like receptor 9 (TLR9). We reported the TLR9 agonist, CpG DNA, mediates exacerbation of disease via the in vitro differentiation of myofibroblasts (1). How TLR9 expression becomes elevated in rapidly progressive IPF and how it regulates myofibroblast function is unknown. We hypothesized that TGF-ß may regulate TLR9 and CpG DNA-stimulated myofibroblasts are profibrotic. Here we tested the effect of TGF-ß on TLR9 and the functional characteristics of CpG DNA-stimulated myofibroblasts.

METHODS: Primary normal human lung fibroblasts (NHLFs) were differentiated in culture with TGF-ß or CpG DNA. Activation of TLR9 was evaluated in lysates by Western Blot analysis of proteolytically cleaved TLR9 (2). The invasive capacity of CpG-DNA-differentiated NHLFs (CpG-NHLFs) was tested using a PDGF-Matrigel invasion assay. Expression of PDGFRs, MMPs, and CD44 was determined. The apoptotic response to hypoxia was examined by cell viability assay, HIF1/HIF 2 expression, and caspase-3 activation.

RESULTS: TGF-ß induces TLR9 expression and activation (Fig. 1). Prolonged stimulation with CpG DNA results in stably differentiated a-SMA+/PDGFRα+/CD44+ myofibroblasts, which acquire invasive capacity through Matrigel. CpG-NHLFs secrete inflammatory cytokines and express increased MMP-14 and activated MMP-2 (Fig. 2). Immunohistochemical analysis of IPF lungs indicates that MMP-14 is upregulated in fibroblastic foci. Moreover, CpG-NHLFs resist hypoxia-induced apoptosis mediated by caspase-3.
**CONCLUSIONS:** TLR9 expression and activation in NHLFs is regulated by TGF-β. CpG DNA induces the differentiation of MMP14+ myofibroblasts, which have an invasive capacity and are resistant to hypoxia-induced apoptosis. These data support a pathway by which CpG-DNA and TLR9 promote rapid disease progression and the onset of other secondary complications such as pulmonary hypertension.

**FIGURE 1.**

![Figure 1](image1)

**FIGURE 2.**

![Figure 2](image2)

Grhl2 Distribution Reveals Novel Patho-physiological Differences Between Human IPF and Mouse Models of Pulmonary Fibrosis

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5. School of Biosciences and Cardiff University, United Kingdom.
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7. Agaplesion Lung Clinic Waldhof-Elgerhausen, Griefenstein, Germany.
8. Universidad Nacional Autónoma de México.

SUMMARY

We recently reported a novel regulatory loop between Grhl2 and Nk2 homeobox (Nkx2-1), which maintains alveolar epithelial cell integrity by directly regulating the composition of adherens and tight junctions. Since chronic injury of alveolar epithelium leads to disruption of epithelial integrity in idiopathic pulmonary fibrosis (IPF), we postulated that GRHL2 is crucial for pathogenesis of this disease and thus may have abnormal distribution. We compared GRHL2 distribution at different stages of human lung development versus IPF and three mouse models of pulmonary fibrosis. GRHL2 is abundant in early and late human fetal as well as adult lung epithelium. However, GRHL2 was detected in normal human lung mesenchyme only at 9 weeks gestation. Similar to this fetal stage, mesenchymal expression of GRHL2 was also observed in IPF. Comprehensive immunofluorescence analysis in serial IPF sections from three patients showed at least two subsets of alveolar epithelial cells (AEC) based on differential
GRHL2 expression and converse fluorescence intensities for epithelial versus mesenchymal markers. In contrast, in bleomycin-induced injury and spontaneously occurring fibrosis in HPS1/2 mutant mice Grhl2 expression was increased in alveolar epithelium, but not expressed in mesenchyme, while in radiation-induced fibrosis, with forced Forkhead box M1 (Foxm1) expression, an overlap of Grhl2 and alpha smooth muscle (alphaSMA) fluorescence was observed in fibrotic regions, suggesting the possibility of alveolar epithelial cell plasticity. The work shows differences in GRHL2 distribution between IPF and mouse models of fibrosis, suggesting a crucial role for GRHL2 in epithelial activation in fibrosis and perhaps also in epithelial plasticity.

Predictors of Mortality and ILD Progression in Scleroderma-Associated Interstitial Lung disease: A Systematic Review

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3Department of Radiology, University of British Columbia, Vancouver, Canada

SUMMARY

OBJECTIVES: Interstitial lung disease (ILD) is the leading cause of morbidity and mortality in patients with systemic sclerosis (SSc), however progression of ILD is variable among these patients and prognostication is challenging. We conducted a systematic review to identify variables that predict mortality and ILD progression in patients with SSc-ILD.

METHODS: A systematic review was conducted using 3 databases to capture all studies relating to predictors of all-cause mortality or ILD progression in SSc-ILD. ILD progression was defined by worsening forced vital capacity or radiological findings of fibrosis. Two authors independently reviewed and extracted data from acceptable studies. Differences were resolved by iteration and consensus.

RESULTS: The initial search identified 3145 unique citations and 167 were reviewed in full text. Twenty-seven studies met inclusion criteria, including 6 abstracts. A total of 1616 patients with SSc-ILD were included, with variable disease duration and ILD severity among studies. Patient-specific, ILD-specific and SSc-specific variables predicted mortality and progression (Figure 1), however most predictors were identified in only one study. Most
studies did not fully account for potential confounders and none of the studies included a validation cohort. Older age, lower FVC and lower DLCO predicted mortality in more than one study. Male gender, extent of disease on HRCT, presence of honeycombing, elevated KL-6 and increased alveolar epithelial permeability were identified as predictors of both mortality and ILD progression on unadjusted analysis. Extent of disease on HRCT was the only variable that independently predicted both mortality and ILD progression.

CONCLUSIONS: Mortality and ILD progression were predicted by several patient-specific, ILD-specific and SSc-specific factors, however few studies have included rigorous analyses that adequately adjust for potential confounders. Additional prospective studies are required to validate these preliminary findings and identify combinations of variables that accurately predict prognosis of SSc-ILD.

FIGURE 1. Predictors of mortality in patients with scleroderma-associated interstitial lung disease. Variables shown in red were independent predictors of mortality in at least one study.
Mesenchymal Stem Cell-Derived Extracellular Vesicles Penetrate Fibrotic Extracellular Matrix and Reverse Fibrosis

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Rady Children’s Hospital of San Diego, San Diego, CA

SUMMARY

OBJECTIVES: Idiopathic pulmonary fibrosis (IPF) is an incurable/fatal disease characterized by (myo)fibroblast differentiation and excessive deposition of extracellular matrix (ECM). Our recent data indicate that mesenchymal stem cell (MSC)-derived extracellular vesicles (mEVs, including exosomes & microvesicles, nano-sized membrane-bound vesicles) can reverse lung fibrosis, representing a novel and powerful therapeutic option. In this study, we further examined the ability of mEVs to penetrate fibrotic matrix in vivo and in vitro.

METHODS: mEVs were isolated from conditioned media (CM) of normal human bone marrow MSC in DMEM. After a series of purification steps, mEVs were characterized by transmission EM (TEM) and nanoparticle tracking analysis (NTA). Using a bleomycin (BL) model of lung fibrosis in mice, we delivered mEVs iv. on D14, and collected lung tissues D21 after BL administration for endpoints including ex vivo experiments.

RESULTS: We found that treatment of fibrotic mice with mEVs significantly modulated ECM collagen deposition and α-smooth muscle actin (αSMA) expression. We also observed migration of labeled mEVs in fibroblast-populated collagen matrices in vitro and in precision-cut lung slices (PCLS) ex vivo from BL-induced fibrotic lung. mEVs were incorporated into Pro-Col1A1 (+) matrices and interacted with αSMA(+) myofibroblasts. Pretreatment of mEVs with hThy1 Ab blocked the incorporation of mEVs into fibrotic lung, suggesting that mEVs Thy-1 may directly engage receptors/ligands, such as integrins, at the recipient cell surface.

CONCLUSIONS: This study suggests direct interaction of mEVs not only with (myo)fibroblastic cells but also with ECM. The ability of mEVs to penetrate fibrotic ECM supports potential therapeutic roles for MSCs or their derivatives in pulmonary fibrosis.

ACKNOWLEDGMENTS: Supported by Pulmonary Fibrosis Foundation & NIH (#HL082818).
The goals of the PFF Summit are to enhance the clinical and scientific knowledge of pulmonary fibrosis in the medical, research, and patient communities. The Pulmonary Fibrosis Foundation (PFF) invited industry researchers to submit abstracts of their scientific research for poster presentation at the PFF Summit 2013: From Bench to Bedside.

Subject matter deemed appropriate for poster presentation at the PFF Summit 2013 include original ideas that will help improve the understanding of pulmonary fibrosis in the following areas:

- Basic Research
- Translational Research
- Clinical Research
- Social Science/Quality of Life Research

Industry posters were not subject to peer review and will not be considered for awards.
Sleep Problems and Quality of Life in Patients with Idiopathic Pulmonary Fibrosis

David Blaser, Bo Katic, Paul Wicks
PatientsLikeMe

SUMMARY

OBJECTIVES: Sleep problems are increasingly common among those with idiopathic pulmonary fibrosis (IPF), and can have a profound negative impact on quality of life (QoL). The aim of this study was to describe the extent and impact of sleep problems experienced by IPF patients participating in an online patient community, PatientsLikeMe.

METHODS: PatientsLikeMe is an online research platform where patients share disease information to accelerate research. In July 2013, a survey was sent to all members, including IPF patients, who had logged in within the previous 90 days to assess their sleep habits. Data was collected on the degree and duration of sleep problems and their impact on QoL. Descriptive statistics were tabulated on the IPF sample, and chi-square and fisher exact testing was used to test for association between categorical variables.

RESULTS: A total of 102 patients with IPF responded to the survey about their sleeping habits. Most (57%) were male, and on average 64 years old (SD: 8.4). A total of 66 IPF patients (65%) reported having or possibly having sleep problems, and 47% of these respondents had sleep problems for between 1 and 5 years. More than half of IPF patients (58.7%) rated the severity of their sleep problems to be moderate, severe, or very severe. Among those who reported sleep problems of some severity level (n=55), more than half (55%) reported that their sleep problems had limited their QoL ‘some’, ‘a lot’, or ‘extremely’ in the past 4 weeks. There was a positive relationship between one’s duration of IPF symptoms and their duration of sleep problems (p=0.02); and a longer duration of sleep problems was significantly associated with a greater negative impact on QoL among IPF patients (p=0.03).

CONCLUSIONS: Sleep problems are fairly prevalent among IPF patients in this sample, and are significantly associated with both IPF symptom duration and decreased QoL. The clinical care of IPF should incorporate treatment of sleep problems to optimize QoL for patients with this disease.
Patient and Pulmonologist Journey with IPF: A Breathtaking Experience

Craig S. Conoscenti¹, Eben M. Rubin¹, Nadia Sapiro²

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²in-sync, Toronto, ON, Canada

SUMMARY

OBJECTIVES: To characterize the IPF journey from the patient and pulmonologist perspective and understand how the patient-pulmonologist relationship can affect the patient journey.

METHODS: A topic guide based on literature was used to stimulate discussion among 61 patients with IPF and 28 pulmonologists in the US. Participants’ experiences were captured using interviews, online methods and written exercises. Data were analyzed for emerging themes using a combination of the grounded theory approach and extended case method.

RESULTS: Patients with IPF experience a unique emotional journey as they adapt to reduced functioning and come to terms with approaching death. The patient journey can be separated into 3 phases. In the separation phase, patients receive the diagnosis of IPF, often after a prolonged period of misdiagnosis in primary care, and are shocked by the poor prognosis. In the transition phase, patients often receive multiple therapies, but may misunderstand their impact due to the unpredictable nature of disease progression. In the reincorporation phase, patients become resigned to their death and its uncertain timing. The pulmonologist journey involves transition from a ‘healer’ to ‘supporter’ role. The journey can be separated into phases of separation, transition and reincorporation, as pulmonologists educate patients according to their expertise, adjust to managing IPF, and become reconciled with a role focused on providing emotional support, symptom management and end of life measures. Four patient typologies and two pulmonologist typologies emerged (Table). The patient-pulmonologist relationship may be affected by their typologies.

CONCLUSIONS: The patient journey in IPF involves coming to terms with the unpredictable course of the disease, accepting reduced physical functioning, and becoming reconciled with the end of their life. The unpredictable course of IPF and lack of effective treatments present unique challenges to pulmonologists, who need to recognize their discomfort with not being able to ‘heal’ these patients, and to consider how best they can support them from diagnosis to the end of their life.

ACKNOWLEDGMENTS: Funded by Boehringer Ingelheim
**TABLE.** Patient and pulmonologist typologies in IPF.

<table>
<thead>
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LPA2/EDG4 is a Therapeutically Relevant Drug Discovery Target for Lung Fibrosis


Celgene Corporation

SUMMARY

Lysophosphatidic Acid (LPA) is a ubiquitous bioactive molecule that plays a role in a wide variety of physiologic and pathophysiologic processes through its family of G-protein coupled receptors (LPA1/EDG2, LPA2/EDG4, LPA3/EDG7, LPA 4, LPA5, LPA6) (1). By modulating fibroblast and epithelial cell activity, LPA and its receptors are believed to be key drivers of and novel therapeutic targets for fibrotic lung disease (2). For example, LPA-dependent effects on fibroblast chemotaxis and epithelial contractility-induced release of latent TGF-beta from extracellular matrix are thought to be mediated by LPA1 and LPA2, respectively (3). The BMS/Amira LPA1-selective antagonist (BMS-986202/AM-152) was reported to have efficacy superior to pirfenidone in animal models of lung fibrosis and is currently in Phase II clinical trials for Idiopathic Pulmonary Fibrosis (IPF) (4). Unlike LPA1, however, the role of LPA2 in lung fibrosis is poorly understood. Here we demonstrate that LPA2 is an important mediator of LPA-dependent cellular activity in both fibroblast and epithelial cell lines. Moreover, we show by immunohistochemistry that LPA2 is upregulated in fibroblastic cells in lung samples from patients with pulmonary fibrosis. Together these results indicate that LPA2 is a therapeutically relevant target in fibrotic lung disease. We also outline a cellular infrastructure developed to support an early stage LPA2 drug discovery campaign and describe how different cell systems can provide important answers but also raise many questions.
A Qualitative and Quantitative Survey of Canadian Patients with Idiopathic Pulmonary Fibrosis: The Emotional Impact of their Experiences with the Diagnostic Process, Diagnosis Disclosure and Current Therapy

Dr. Diane Gajewczyk, PhD, MBA & Dr. Charles K.N. Chan, MD, FRCPC, FCCP, FACP
InterMune Canada Inc.

SUMMARY

OBJECTIVES: Idiopathic pulmonary fibrosis (IPF) is a rare, progressive, irreversible chronic lung disease. This study evaluated how the diagnostic process, diagnosis disclosure and perceptions regarding current therapies impacted emotional well-being of IPF patients and their ability to cope with the disease. Unmet needs and areas for improvement in IPF care were identified.

METHODS: In Phase-I, 10 in-depth interviews of 1-to-1.5 hr duration were conducted by research specialists in homes of IPF patients (in Vancouver, Toronto and Montreal) between February and August 2012. Based on results, a quantitative questionnaire was designed and self-administered online by 63 IPF patients located across 5 Canadian provinces. Patients were recruited from Canadian IPF foundation, Ontario Lung association and respirologists from regional IPF centres.

RESULTS: There was large variability in the time it took to make the correct diagnosis, ranging from less than 1 month to 10 years (average 11 months from first consultation with physician). Only 32% of respondents received IPF as their first diagnosis. Typically, patients saw 2-3 different doctors and undertook multiple tests. Time-to-diagnosis varied by patient demographic and was delayed in males younger than 68, with lower levels of education who suffered chronic symptoms with a more insidious onset. Half of respondents were dissatisfied with how the diagnosis was disclosed to them and 1-in-3 asked for a second opinion. Most patients received treatment for IPF (mostly corticosteroids, acetylcysteine/Mucomyst or azathioprine) but were dissatisfied with the efficacy. 27% were never treated and of these 24% were extremely concerned that they were not being treated. Patients who had access to tier 1/2 specialized centres had higher satisfaction with their care than those who did not have the access.

CONCLUSIONS: There is a need to improve the diagnostic process and shorten the time to correct diagnosis of IPF. Respirologists should become aware of the profound impact of psychological aspects, such as the way IPF diagnosis is disclosed, on long-term well-being of the patient. Also, more information about available treatment options should be given and a referral to tier 1/2 care centre should be made whenever possible.
FIGURE 1: On average, the diagnostic process takes 11 months from first contact with a doctor. 

FIGURE 2: There are clear differences in perceived level of care between those who are managed in tier 1 or tier 2 centres and those who are not.
ACKNOWLEDGEMENTS: The survey was sponsored by InterMune International AG. CC received an honorarium from InterMune. DG is an employee of InterMune.

REFERENCE LIST:
Lebrikizumab Idiopathic Pulmonary Fibrosis Trial: A Phase II Randomized, Double-blind, Placebo Controlled Study to Assess Efficacy and Safety (RIFF)

Belloni P, Gershman A, Ackrill A, Doyle R, Katugampola L, Kaminski J,
Genentech Inc., South San Francisco, CA

SUMMARY

OBJECTIVES: Lebrikizumab is a humanized monoclonal IgG antibody targeting the cytokine interleukin-13 (IL-13). Lebrikizumab binds specifically to soluble IL-13 and blocks signaling through the interleukin-4R alpha (IL-4Ra)/IL-13Ra1 pathway, thereby preventing the downstream effects of human IL-13 with high potency. The IL-13 and IL-4 pathway have been implicated in normal tissue repair processes and aberrant lung fibrosis. IL-13 and IL-4 are strong inducers of fibrogenic responses in vitro and tissue fibrosis in vivo. Idiopathic pulmonary fibrosis (IPF) is characterized by varying degrees of interstitial fibrosis. It is hypothesized that inhibition of IL-13 by lebrikizumab may reduce disease progression. Based on the importance of IL-13 in the pathogenesis of IPF, inhibition of IL-13 represents a potentially effective approach for the treatment of patients with a confirmed diagnosis of IPF across a broad range of disease severity.

METHODS: LebRikizumab Idiopathic Pulmonary Fibrosis Trial: A Phase II Randomized, Double-Blind, Placebo-Controlled Study to Assess Efficacy and Safety, (RIFF), is designed to evaluate the safety and efficacy of lebrikizumab in patients with Idiopathic Pulmonary Fibrosis. The trial sets out to enroll 250 patients with a confirmed definite IPF diagnosis based upon HRCT and surgical lung biopsy (if available). Patients will be randomized 1:1 to lebrikizumab or placebo and treated for a minimum of 48 weeks. Inclusion/Exclusion criteria have been established to include patients across a broad range of disease severity. The study will measure safety, efficacy, functional, structural and quality of life outcomes over a maximum period of 2.5 years. The primary outcome measure for the study is Progression Free Survival. A number of design features distinguish this trial, among them are the inclusion of patients across a broad range of disease severities, standardization of lung function including DLco, and assessment of patient activity using biosensor technology. A fully integrated biomarker program is planned to assess pre-selected serum proteins as candidate biomarkers prognostic of disease progression and predictive of treatment benefit.

CONCLUSION: Further information is available at www.clinicaltrials.gov
A Qualitative Survey of European Patients with Idiopathic Pulmonary Fibrosis: Physical and Emotional Impact of the Disease and Perceptions of Current Therapy

Vancheri C.1, Russell A.M.2, Maronati M.3, Giot C.3
1 University of Catania, Catania Italy
2 Royal Brompton Hospital, London United Kingdom
3 Intermune IAG, Muttenz Switzerland

SUMMARY

OBJECTIVES: Idiopathic pulmonary fibrosis (IPF) is a rare, progressive, irreversible chronic lung disease, with a median survival time of 2–5 years1-4. This study aimed to explore the impact of IPF on patients at both a physical and emotional level and to evaluate the patients' experience of pirfenidone, the first approved treatment for IPF.

METHODS: Patients with a physician-confirmed diagnosis of IPF and currently on pirfenidone therapy were enrolled in a qualitative survey. One-to-one in-depth interviews of 1 hr duration were conducted by research specialists in three European countries (Germany, Italy, and the United Kingdom) between September 24th and October 19th 2012.

RESULTS: Patients (N=45; 71% male) had a mean age of 68.5 years, with a mean time since diagnosis of 3.5 years. Most patients perceived that IPF caused substantial functional limitations in their lives (56%). Fatigue was reported as the main symptom that generated physical limitations (82%), with loss of appetite, coughing, difficulty lifting objects, and disturbed sleep also cited (Figure 1). At the emotional level, a strong majority of patients experienced fear about the future (72%), while patients also reported frustration and anger (36%), and social isolation (18%) (Figure 2). IPF also impacted family and caregivers. Information about IPF, including the use of pirfenidone in IPF, and updates on new research and treatment for IPF, was sought by 74% of patients. As the first treatment available for IPF, patient’s experiences of pirfenidone therapy were positive overall (average patient satisfaction rating of 7.4 out of 10). Patients experiencing side effects due to the therapy cited needing more reassurance regarding the efficacy profile of the drug.

CONCLUSIONS: For the majority of patients, a diagnosis of IPF had a major physical and emotional impact. Psychological support for both patients and their families should become an integral part of the management of the disease. The availability of the first treatment for IPF, pirfenidone, was perceived by patients to offer hope and reassurance for the future, although improved management of side effects is still needed. Clearer information on IPF, drug treatment benefits, and potential side effects should also be made available.
FIGURE 1: The main symptoms spontaneously reported by patients with IPF leading to physical limitations

![Figure 1](image1)

FIGURE 2: The emotional impact of living with IPF spontaneously reported by patients

![Figure 2](image2)

ACKNOWLEDGEMENTS: The survey was sponsored by InterMune International AG. CV and AMR have received honoraria from InterMune. MM and CG are employees of InterMune.

REFERENCE LIST:
Inhibition of TGF-ß Signalling and LOXL2: Pharmaxis’ Double Pronged Small Molecule Approach to Treat Fibrosis

Pharmaxis Ltd.

SUMMARY

OBJECTIVES: Idiopathic pulmonary fibrosis (IPF) is a progressive disease that is predominately driven by transforming growth factor ß (TGF-ß), interleukin 6 (IL-6) and tumour necrosis factor a (TNF-a) that cause extensive scarring, inflammation and airway remodelling. In particular TGF-ß stimulated fibroblasts differentiate into myofibroblasts and contribute to fibrosis by producing extracellular matrix components like collagen, elastin and fibronectin and their cross-linking enzyme lysyl oxidase like 2 (LOXL2). Pharmaxis has developed a mannose-6-phosphate analogue, PXS64, that inhibits TGF-ß1 signalling in fibroblasts and a small molecule LOXL2 inhibitor, PXS-5033A, which was tested in various in vitro and in vivo models of fibrosis.

METHODS: The effects of PXS64 on TGF-ß1 signalling were studied in cell cultures from human lung fibroblasts using Western blots and proteomic analysis. Lysyl oxidases from human and rat were isolated and the enzymatic inhibition of PXS-5033A was tested in an Amplex Red assay. Its effects were then analysed in vivo by a reduction in picrosirius red stain in a mouse model of fibrosis.

RESULTS: PXS64 inhibited the TGF-ß1 induced accumulation of collagen and fibronectin in human fibroblasts from an immortal cell line (HF19) and primary culture (NHLF cells from Lonza). In fibroblasts from IPF patients, PXS64 improved the phenotype to regular fusiform, healthy shaped and reduced the production of matrix proteins. Proteomic analysis showed a specific inhibition of the TGF-ß pathway. PXS-5033A concentration-dependently inhibited human LOXL2 activity 100 fold more potent that LOX activity. PXS-5033 has drug like properties and reduced the extent of fibrotic area in a mouse model of fibrosis when dosed therapeutically, similar to treatment with imatinib.

CONCLUSIONS: PXS64 and PXS-5033A are two small molecules that inhibit fibrosis at different stages of the signalling cascade.
Pulmonologist Perspective on the Diagnosis and Treatment of Idiopathic Pulmonary Fibrosis Patients

Jeanne Loboda, Shikha Garg
InterMune, Inc.

SUMMARY

INTRODUCTION: Idiopathic pulmonary fibrosis (IPF) is a progressive disease that causes scarring and thickening of the lungs. Over time, the lungs lose their ability to effectively expand and transmit oxygen into the bloodstream, causing a range of symptoms, including dry cough and dyspnea. The current study aimed to characterize the diagnosis and treatment of IPF from the physician's perspective.

METHODS: 300 US-based pulmonologists were engaged in an online survey to determine their perspectives on referral patterns, timing of diagnosis, disease severity at diagnosis, treatments for IPF, disease progression characteristics, and desired attributes of treatments for IPF.

RESULTS: Most IPF patients were referred to pulmonologists from primary care physicians. Sixty-one percent were referred without a confirmed diagnosis of IPF. Pulmonologists believe IPF patients were diagnosed an average of 8.4 months after their first symptoms, and their disease was mainly defined as moderate (41%) or severe (33%). Only 23% of IPF patients were deemed to be rapidly progressing, with most progressing slowly or very slowly. The most common treatments for IPF were pulmonary rehabilitation and oxygen, bronchodilator combinations, and N-acetylcysteine (NAC). The most important attribute of a treatment for IPF was the ability to slow disease progression.

CONCLUSION: IPF patients are often referred by their primary care physicians to the pulmonologist without a definitive diagnosis of IPF. Almost three-quarters have moderate to severe disease and are most commonly treated with pulmonary rehabilitation and oxygen, bronchodilator combinations, and NAC. The most important attribute of a treatment for IPF is the ability to slow disease progression.

Inhibition of ATP-gated P2X3 Channels by AF-219: an Effective Anti-tussive Mechanism in Chronic Cough

Afferent Pharmaceuticals

SUMMARY

OBJECTIVE: Pre-clinical studies suggest that P2X3 receptors are expressed by airway vagal afferents and contribute to the hyperexcitability of sensory neurons. We hypothesized that P2X3 receptors play a role in the sensitisation of vagal pathways mediating the cough reflex leading to chronic cough (CC). We therefore investigated the efficacy of a first in class oral P2X3 antagonist, AF-219, in reducing daytime cough in idiopathic/treatment-resistant CC.

METHODS: 24 subjects (19 women, mean age 54.5 years) were randomised into a double blind, placebo-controlled, 2-period, crossover study, of AF-219, 600 mg bd. Cough was assessed at baseline and after 2 weeks of treatment; primary endpoint, daytime objective cough frequency (coughs/hr) (VitaloJAK™); secondary endpoints, cough severity and urge to cough visual analogue scales (VAS), cough quality of life questionnaire (CQLQ).

RESULTS: AF-219 markedly reduced cough (mean difference vs. placebo): daytime cough rate -75% (95%CI -50 to -88), p< 0.001 (Figure 1); daytime cough severity VAS -26mm (-10 to -42), p=0.003; urge to cough VAS -21mm (-2 to -41), p=0.035; and CQLQ -9.2 (-1.7 to -16.8), p=0.018. There were no significant period or carryover effects.

CONCLUSION: P2X3 receptors appear to play a key role in mediating cough neuronal hypersensitivity and their antagonists represent a promising new class of effective anti-tussives.

DISCLOSURES: The study was funded and sponsored by Afferent Pharmaceuticals, Inc.
R. Abdulqawi: University of Manchester-employed sub-investigator for this Afferent Pharmaceuticals-funded study
R. Dockry: University of Manchester-employed research assistant for this Afferent Pharmaceuticals-funded study
K. Holt: University of Manchester-employed research assistant for this Afferent Pharmaceuticals-funded study
A. Woodcock: No disclosures related to Afferent
G. Layton: Consultant to Afferent Pharmaceuticals
B. McCarthy (presenting author): employee of Afferent Pharmaceuticals
A.P. Ford: employee of Afferent Pharmaceuticals
J.A. Smith: University of Manchester-employed principal investigator for this Afferent Pharmaceuticals-funded study
Comparison of BALF and Blood Biomarkers in a Single-center Cross Sectional Phase 0 Study of IPF and Control Subjects

Anne Minnich, Sanjay Keswani, Scott Palmer, Matthew Foster, Arthur Moseley, Robert Townsend, and Claudio Pasquinelli
Bristol-Myers Squibb

SUMMARY

INTRODUCTION: Despite a wealth of recent literature on the topic of circulating biomarkers associated with disease progression and severity in Idiopathic Pulmonary Fibrosis (IPF), relatively few studies have directly compared levels of these biomarkers in bronchoalveolar lavage fluid (BALF) and blood.

METHODS: We conducted a small single center cross sectional study in order to compare levels of biomarkers between IPF and control subjects, designed to minimize heterogeneity among the former in order to maximize chances of observing differences between groups. Subjects with IPF (n=4), strictly defined according to ATS criteria and with FEV1/FVC >0.75 and control subjects (n=5), were recruited at Duke University. Eligibility criteria were stringent (e.g. FEV1/FVC >0.75). The following analyses were performed: serum, plasma, and BALF supernatant soluble markers, BALF supernatant proteomics, BALF cell pellets and whole blood gene expression, and BALF cell and PBMC flow cytometry. In addition, we compared BALF biomarker levels between right middle and right lower lobes of the lung.

RESULTS: Results indicated marked differences between IPF and control subjects for biomarkers associated with disease progression (e.g. MMP-7, SP-D, MUC1, S100A12 and others), in all compartments studied. Correlations indicated differences in blood-BALF relationships among lung injury biomarkers; for example, SP-D and MUC1 displayed opposite relationships between BALF and serum levels. Other biomarkers were significantly correlated to lung function parameters, e.g. BALF VEGF and DLCO. Proteomics revealed higher BALF levels of MUC5b in IPF compared to control subjects. The data will guide biomarker strategy for our Phase 2 study of an LPA1 antagonist in IPF.

ACKNOWLEDGEMENTS: Clinical Biomarkers and Imaging Immunology, Bristol-Myers Squibb, Duke University/Proteomics Core Facility
Functional Respiratory Imaging (FRI): Insight Into Regional Characteristic of Idiopathic Fibrotic Lungs

Jan De Backer, Lieven Nuyttens
FluidDA Inc

SUMMARY

BACKGROUND: Idiopathic Pulmonary Fibrosis (IPF) is characterized by the occurrence of fibrotic tissue thereby restricting the pulmonary function. It has proven very challenging to identify outcome parameters, using the conventional pulmonary function tests (PFT), which are useful in clinical trials to assess the efficacy of novel compounds.

STUDY AIM: The current study aims to use novel imaging tools, FRI, to assess the pulmonary function of an IPF patient and compare the pathophysiology of this patient with a healthy volunteer and a chronic obstructive pulmonary disease (COPD) patient.

METHODS: FRI is a combination of high-resolution CT images and Computational Fluid Dynamics. The latter, which originates from the aerospace industry, yields regional resistance measurements. In all three subjects a low dose CT scan was taken at functional residual capacity (FRC) and at total lung capacity (TLC). FRI provides airway geometry down to the level of the smaller airways with a diameter of 1-2mm. In addition lobar volumes can be calculated at FRC and TLC and subsequently in the internal airflow distribution can be determined.

RESULTS: The PFT results for the three subjects were:

- Healthy volunteer (43yo F, 169cm, 73.2kg): FEV1=110%p; FEV1/VC=84%; FRC=92%p; sRaw=0.81kPas.
- COPD patient (71yo M, 168cm, 62.9kg): FEV1=44%p; FEV1/VC=28%; FRC=139%p; sRaw=3.05kPas
- IPF patient (79yo F, 154cm, 68kg): FEV1=99%p; FEV1/VC=80%; FRC=57%p; sRaw=0.66kPas

FRI clearly showed the stark differences between the healthy subject, the obstructive disease (COPD) and the restrictive disease (IPF). Lobar volumes in the IPF patient were all under inflated compared to the healthy reference values, while the COPD patient was significantly hyper inflated (Figure 1). Interestingly the volume of IPF patients airway (siVaw) was considerably larger compared to the healthy subject and the COPD patient (Figure 2).
CONCLUSION: FRI is promising tool to gain further insight into the pathophysiology of IPF and provides the potential for clinically relevant biomarkers, which could be used as endpoints in clinical trials.

FIGURE 1: FRC-based lobar volumes at FRC and TLC for a healthy, IPF and COPD subject

FIGURE 2: Airway volume, Airway radius and airway resistance in healthy, COPD and IPF subject determined using FRI
High Baseline Serum Lysyl Oxidase Like-2 (sLOXL2) Levels are Associated with Higher Risk for Idiopathic Pulmonary Fibrosis (IPF) Disease Progression and Mortality

Jason Chien, MD, MS1; Thomas Richards, PhD3; Kevin Gibson, MD3; Yingze Zhang, PhD3; Kathleen Lindell PhD, RN3; Lixin Shao, MD, MS2; Susan Lyman, PhD2; Joanne Adamkewicz, PhD2; Victoria Smith, PhD2; Naftali Kaminski, MD3; Thomas O’Riordan, MD3

1Gilead Sciences, Inc. Seattle WA/US and 2Foster City, CA/US; 3The Dorothy P. and Richard P. Simmons for Interstitial Lung Disease, University of Pittsburgh, PA/US

SUMMARY

RATIONALE: In pulmonary fibrosis, LOXL2 promotes cross-linking of collagen, driving matrix remodeling and formation of pathologic stroma. We hypothesized that sLOXL2 levels may reflect IPF disease activity.

METHODS: Serum and clinical data from ARTEMIS-IPF NCT00768300 (n=67) and the Genomic and Proteomic Analysis of Disease Progression in IPF (GAP) study (n=104) were analyzed. sLOXL2 levels were quantified using a proprietary LOXL2 ELISA assay. Disease progression (DP), which includes lung function (LF) decline (10% decrease in FVC and 5% decrease in DLCO or 15 % decrease in DLCO and 5% decrease in FVC), respiratory hospitalizations (RH) and mortality, served as the primary endpoint for ARTEMIS-IPF. DP without RH was applied to the GAP analysis. A classification and regression trees (CART) method was used to select the optimal thresholds for dichotomization of sLOXL2 levels in each cohort.

RESULTS: In comparison to ARTEMIS-IPF, GAP patients had higher sLOXL2 levels: medians 324pg/mL (interquartile range [IQR] 147, 770) versus 716pg/mL (IQR 358, 1447). Although sLOXL2 correlated weakly with baseline FVC and DLCO (r range -0.25 to 0.05) in both cohorts, sLOXL2 levels were significantly associated with IPF outcomes (Table). CART-determined thresholds were similar: 800pg/mL in ARTEMIS-IPF and 700pg/mL in GAP. In ARTEMIS-IPF, high sLOXL2 (>800pg/mL) was associated with higher risk for DP (HR 5.4, 95% confidence interval [CI] 1.7-17.7, p=0.005). This effect was mainly driven by lung function decline (HR 7.6, 95% CI 1.2-48.3, p=0.031, and RHs (HR 5.4, 95% CI 1.2-24.0, p=0.029), with a trend toward higher risk for death (HR 1.9, 95% CI 0.3-12.4, p=0.517). Among GAP patients with baseline spirometric data (n=70), high sLOXL2 levels (>700pg/ml) were associated with more DP events at
24-months after enrollment (HR 1.8, 95% CI 1.0-3.1, p=0.045). When all GAP patients were included, high sLOXL2 levels were associated with higher risk for mortality at 24-months after enrollment (HR 2.2, 95% CI 1.1-4.2, p=0.019).

**CONCLUSIONS:** sLOXL2 levels appear to be a prognostic biomarker for IPF disease outcome.

**TABLE**

![Diagram showing disease progression and death in ARTEMIS-IPF and GAP, comparing high and low sLOXL2 levels.](chart)
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)

T. Chew¹, S. Frye¹, M. Klemsz¹,², W. Lange¹, K. Rothhaar¹,², D. S. Wilkes¹,²

¹ImmuneWorks Inc, USA; ²Indiana University School of Medicine, USA

SUMMARY

INTRODUCTION: IPF displays many characteristics of an immune disease as evidenced by presence of B and T cell responses to specific antigens and the presence of lymphocyte aggregates in the lungs of patients with IPF. ImmuneWorks scientists hypothesize that lung injury results in the exposure of type V collagen (col(V)) a protein normally hidden from the immune system. The immune system recognizes this sequestered protein as foreign, initiating an autoimmune cascade, resulting in an attack on the lung. As the autoimmune response expands, a fibrotic response would follow in an attempt to heal the lung. As tremendous heterogeneity is observed in IPF disease process and progression, we believe that autoimmunity against col(V) status may identify an important subset of IPF patients who experience faster lung function decline and increased incidence and severity of BOS after lung transplant. IW001 is an oral solution of col(V), therapeutic agent in clinical development for IPF patients with ongoing anti-col(V) immunity. The therapeutic use of IW001 is to down-regulate the immune response against col(V) and stop further progression of fibrosis.

METHODS: ImmuneWorks, Inc. conducted an open label, multicenter, phase I clinical trial in IPF patients who tested positive for anti-col(V) antibodies. This study was designed to evaluate the safety, tolerability, and biological/clinical effects of a three doses (0.1mg, 0.5mg, 1.0mg) of IW001, when administered once daily orally for 24 weeks. Lung function was measured at screening, 12 week and 24 weeks.

RESULTS: 30 IPF patients were enrolled in the three IW001 treatment groups. IW001 was well tolerated with no unexpected adverse events. Absolute changes in %FVC predicted showed a trend toward the stabilization of the lung function with both 0.5mg and 1.0mg/day of IW001. Changes in biomarkers such as MMP7 and C1q supported the therapeutic impact of IW001 in the stabilization of FVC.

CONCLUSIONS: The results of this clinical trial demonstrated that IW001 is well tolerated. Favorable trends in the levels of two biomarkers coinciding with stabilized lung function were observed in the middle and highest doses tested. Collectively these data provide the rationale for advancing IW001 into phase 2 trials.
Extended Treatment of Idiopathic Pulmonary Fibrosis with Anti-CTGF Monoclonal Antibody FG-3019: Interim Results of Phase 2 Clinical Trial

Ganesh Raghu1, Mary Beth Scholand2, Yolanda Mageto3, Jonathan Goldin4, Seth Porter5, Thomas Neff5, Frank Valone5, Loredie Lugos5, John Stauffer5

1University of Washington, Seattle, Washington; 2University of Utah, Salt Lake City, Utah; 3University of Vermont, Burlington, Vermont; 4David Geffen School of Medicine, Los Angeles, California; 5FibroGen, Inc., San Francisco, California.

SUMMARY

INTRODUCTION: Connective tissue growth factor (CTGF), a central mediator of fibrosis, is implicated in the pathogenesis of IPF. FG-3019, a novel anti-fibrotic agent, attenuates CTGF activity and is a potential therapy for IPF.

OBJECTIVES: To evaluate the safety, tolerability, and efficacy of FG-3019 in subjects with IPF.

METHODS: FG-3019 (15 mg/kg every 3 weeks x 45 weeks) was administered to 53 subjects with well-defined mild to severe IPF (Cohort 1). FVC was measured every 12 weeks and quantified HRCT scores of whole lung fibrosis and interstitial lung disease were obtained at baseline and weeks 24 and 48. Nineteen subjects with less than 3% decline in FVC percent predicted in the first year received extended treatment in a second year (Cohort 1-EX, ongoing).

RESULTS: FG-3019 has been well tolerated in the first and second years of treatment. No drug-related SAEs have been reported. Quantified interstitial lung disease (QILD) scores (sum of changes in reticular fibrosis, ground glass, and honeycombing) at week 48 showed improvement or stability in 20 of 38 (53%) Cohort 1 subjects. Changes in QILD from baseline were significantly associated with changes in FVC percent predicted at weeks 24 (p<0.001) and 48 (p<0.04). Subjects with improved/stable QILD at weeks 24 and 48 had significantly smaller changes in FVC % predicted than subjects with worsened QILD (p<0.05). Week 24 QILD changes were predictive of fibrosis, QILD, and FVC % predicted changes at week 48. Thirteen of 19 (68%) Cohort 1-EX subjects have demonstrated improved or stable FVC to date.

CONCLUSIONS: The safety and tolerability profile of FG-3019 is excellent over 2 years of treatment. The HRCT QILD score demonstrated improvement or stability in more than half of subjects with moderate to severe IPF treated with FG-3019. The potential of quantified HRCT QILD score as a biomarker to assess outcomes of IPF treatment with FG-3019 appears promising. Over two-thirds of patients eligible for extended treatment with FG-3019 have improved or stable lung function in the extended treatment year.
Exploratory Efficacy Evaluation of PRM-151 in Patients with Idiopathic Pulmonary Fibrosis

EG Trehu, MD\(^1\), B van den Blink, MD, PhD\(^2\), J Burggraaf, MD, PhD\(^3\), LD Morrison, MD\(^4\), LC Gins, MD\(^5\), MS Wijnenbeek, MD, PhD\(^2\), M Moerland, PhD\(^3\), MR Dillingh, MSc\(^3\)

\(^1\)Lexington, MA/US, \(^2\)Rotterdam, The Netherlands, \(^3\)Leiden, The Netherlands, \(^4\)Durham, NC/US, \(^5\)Boston, MA/US

Promedior

SUMMARY

BACKGROUND/RATIONALE: Idiopathic pulmonary fibrosis (IPF) is a progressive, debilitating, fatal restrictive lung disease. PRM-151 is a recombinant form of Pentraxin-2, an endogenous human protein that binds to monocyte Fc-gamma receptors, promotes their differentiation into regulatory macrophages, promoting epithelial healing and resolution of inflammation and scarring, and prevents differentiation into M2 pro-fibrotic macrophages and fibrocytes, preventing fibrosis. Therapeutic dosing of Pentraxin-2 and PRM-151 reduced fibrosis in TGF-ß1 and bleomycin pre-clinical models of lung fibrosis.

METHODS: In this prospective, randomized, double-blind, placebo-controlled, multiple ascending dose Phase I clinical trial in adults with IPF, PRM-151 (PRM) or placebo (pl) was administered on days 1, 3, 5, 8, and 15 by 30 minute IV infusion to three successive cohorts of patients (1 mg/kg: 6 PRM/2 pl; 5 mg/kg: 5 PRM/2 pl; 10 mg/kg: 4 PRM/2 pl). Safety, immunogenicity, pharmacokinetics and exploratory efficacy endpoints were assessed through Day 57.

RESULTS: PRM-151 was well tolerated at all dose levels, with linear increase in Cmax and AUC48h with increasing doses and t 1/2 32.8 hours. Common adverse events were cough, productive cough, fatigue, headache and dyspnea, equal in PRM and pl treatment groups. No serious events were reported; PRM antibodies were not detected. Baseline pulmonary function was worse in placebo group, with no correlation between baseline FVC % predicted and outcome. There was a trend towards improvement in FVC % predicted in the combined PRM-151 group (Table 1). Three of 14 evaluable patients had 10% increase from baseline in FVC % predicted (Figure 1), with concurrent improvement in 6 minute walk test (6MWT) and St. George's Respiratory Questionnaire (SGRQ) in 2/3. Three patients had 5% increase from baseline in FVC % predicted, with concurrent improvement in DLCO in 2/3 and 6MWT and SGRQ in one each. No placebo patients had 5% increase from baseline FVC % predicted.
CONCLUSIONS: PRM-151, administered 5 times over 15 days, was well tolerated at 1, 5 and 10 mg/kg. PRM-151 treatment at all doses resulted in a trend towards improvement of pulmonary function at 8 weeks. Further investigation of PRM-151 in IPF is warranted.

**TABLE 1.** Change in pulmonary function tests and 6 minute walk distance from baseline to day 57

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>PRM-151 mean, (SD)</th>
<th>Placebo mean, (SD)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent Predicted FVC (absolute change in %)</td>
<td>+2.4 (4.0)</td>
<td>-1.5 (3.3)</td>
<td>0.054</td>
</tr>
<tr>
<td>DLCO (absolute change in %)</td>
<td>-1.8 (4.79)</td>
<td>-2.3 (2.1)</td>
<td>0.80</td>
</tr>
<tr>
<td>6 Minute Walk Test (meters)</td>
<td>+8 (51)</td>
<td>-10.5 (51)</td>
<td>0.47</td>
</tr>
<tr>
<td>SGRQ Total</td>
<td>+1.0 (13.1)a</td>
<td>-0.5 (6.2)b</td>
<td>0.80</td>
</tr>
</tbody>
</table>

a. N=12 for SGRQ
b. N=5 for SGRQ

**FIGURE 1.** Relative change from Baseline on Day 57 in FVC% Predicted
Hospitalization and Exacerbation Patterns and the Associated Burden among Patients Newly Diagnosed with Idiopathic Pulmonary Fibrosis

Ning Wu, PhD¹, Yanni Yu, MA, MS², Chien-Chia Chuang, MSc, MAE, PhD³, Rosa Wang, MHA¹, Nicole Benjamin, BS³, David Coultas, MD³

¹Evidera, Lexington, MA
²Boehringer Ingelheim, Ridgefield, CT
³University of Texas Health Science Center at Tyler, Tyler, TX

SUMMARY

OBJECTIVE: To assess the patterns of hospitalizations and exacerbations resulting in hospitalizations (inpatient exacerbations) or urgent care visits (urgent-outpatient exacerbations) and associated costs.

METHODS: A national commercial claims database (2006-2011) was analyzed. Newly-diagnosed IPF patients were identified with 2+ claims for idiopathic interstitial pneumonia (ICD-9-CM 516.3x) after lung biopsy or thoracic high resolution computed topography scan. All study outcomes were measured within one year after the initial diagnosis of IPF. Rates of hospitalizations, IPF-related hospitalizations, and inpatient exacerbations were calculated. IPF-related hospitalizations were hospitalizations with primary diagnosis of 516.3x or primary diagnosis of respiratory failure and secondary diagnosis of 516.3; inpatient exacerbations were a subgroup of IPF-related hospitalizations, without diagnoses of respiratory infection, heart failure, pulmonary embolism, or pneumothorax dated within ±15 days of the hospitalization. Urgent-outpatient exacerbations were defined as emergency room visits or urgent/unscheduled physician visits with a diagnosis of 516.3x and without diagnoses of respiratory infection, heart failure, pulmonary embolism, or pneumothorax. Healthcare costs associated with exacerbations were estimated.

RESULTS: Of 1,735 IPF patients (mean [SD] age: 72 [13] years; male: 54.0%), 38.7% had hospitalizations, 10.8% had IPF-related hospitalizations, and 4.6% had inpatient exacerbations. On average, an inpatient exacerbation lasted 6 days (SD:7; median=4) with an average cost of $14,731 (SD=$85,468; median=$2,213). 72.1% of the IPF patients had urgent-outpatient exacerbations, which occurred most frequently in the first quarter after the initial diagnosis. An IPF patient had an average of 2.3 urgent outpatient exacerbations (SD:2.6); the average cost per urgent-outpatient exacerbation was $444 (SD:$1,481; median=$176).
CONCLUSION: IPF-related hospitalizations and exacerbations were common among patients newly diagnosed with IPF. The majority of exacerbations occurred within the first 90 days after the initial diagnosis and were associated with high costs. These results suggest a need for treatments to help reduce exacerbations among patients with IPF.

TABLE 1. Proportion of newly-diagnosed IPF patients with hospitalizations, IPF-related hospitalizations, and exacerbations resulting in hospitalizations

<table>
<thead>
<tr>
<th>% of all IPF patients (N=1,735)</th>
<th>Time to the first event in days, among IPF patients with the event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalizations</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>38.7%</td>
<td>92.7 (99.8)</td>
</tr>
<tr>
<td>IPF-related hospitalizations</td>
<td>10.8%</td>
</tr>
<tr>
<td>Inpatient exacerbations</td>
<td>4.6%</td>
</tr>
</tbody>
</table>

FIGURE 1. Proportion of newly-diagnosed IPF patients with exacerbations resulting in urgent outpatient visits by quarter after initial IPF diagnosis
scientific sessions

OPENING SESSION KEYNOTE ADDRESS (NOT CERTIFIED FOR CME)
Robert J. Beall, PhD
President and CEO, Cystic Fibrosis Foundation
LUNG INJURY AND REPAIR

LEADERS: Gregory P. Cosgrove, MD; Martin Kolb, MD, PhD; Patricia J. Sime, MD

INTRODUCTION: LUNG INJURY AND REPAIR
Gregory P. Cosgrove, MD

To download presentation slides, please visit www.pffsummit.org/slides.html.
LUNG INJURY AND REPAIR

TARGETING MATRIX: OPPORTUNITIES FOR THERAPY
Patricia J. Sime, MD

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LUNG INJURY AND REPAIR

ROLE OF ALVEOLAR EPITHELIUM IN PULMONARY FIBROSIS:
INNOCENT Bystander OR ACTIVE PARTICIPANT?
Zea Borok, MD
LUNG INJURY AND REPAIR

IPF FIBROBLASTS AND THEIR CELL-OF-ORIGIN
Craig Henke, MD

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CELL BASED THERAPY TO CORRECT THE TISSUE MILLEU IN IPF
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LUNG INJURY AND REPAIR

PANEL DISCUSSION

LEADER: Martin Kolb, MD, PhD

PANEL: Gregory P. Cosgrove, MD; Patricia J. Sime, MD; Zea Borok, MD;
Brigitte Gomperts, MD; Craig Henke, MD

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SPECIAL LUNCHEON SPEAKER

WHEN DRUG RESEARCH IS PERSONAL: THE IMPORTANCE OF PATIENT ADVOCACY IN DRUG DEVELOPMENT AND INNOVATION

John F. Crowley, JD, MBA, Chairman and CEO, Amicus Therapeutics

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PERSONALIZED MEDICINE: GENETICS AND BIOMARKERS

LEADER: Fernando J. Martinez, MD, MS

INTRODUCTION: GENETICS AND BIOMARKERS
Fernando J. Martinez, MD, MS
PERSONALIZED MEDICINE: GENETICS AND BIOMARKERS

GENETIC MARKERS: IMPACT ON OUTCOME AND PATIENT MANAGEMENT
Christine Kim Garcia, MD, PhD

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GENOME-WIDE APPROACH TO A PERSONALIZED SURVIVAL IN IPF
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Janet Talbert, MS, CGC

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PERSONALIZED MEDICINE: GENETICS AND BIOMARKERS

PANEL DISCUSSION
LEADER: Fernando J. Martinez, MD, MS
PANEL: Christine Kim Garcia, MD, PhD; Imre Noth, MD; Ivan O. Rosas, MD

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DRUG DEVELOPMENT IN IPF (NOT CERTIFIED FOR CME)

LEADERS: A. Bruce Montgomery, MD; Dean Sheppard, MD

INTRODUCTION: COMPARISON OF REGULATORY AGENCIES AND THE APPROVAL PROCESS
A. Bruce Montgomery, MD

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Tom O’Riordan, MD

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DRUG DEVELOPMENT IN IPF (NOT CERTIFIED FOR CME)

PANEL DISCUSSION

PANEL: A. Bruce Montgomery, MD; Dean Sheppard, MD; Ritu S. Baral; Williamson Bradford, MD, PhD; Alan H. Cohen, MD; Tom O’Riordan, MD; Eugene J. Sullivan, MD; Shelia Violette, PhD

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clinical sessions

LEADERS: Kevin R. Flaherty, MD, MS; Marvin I. Schwarz, MD; Jeffrey James Swigris, DO, MS; Leslie C. Watters, MD

POSTER ABSTRACT PRESENTATIONS
Jesse Roman, MD; Michael F. Beers, MD
SESSION INTRODUCTION
Jeffrey James Swigris, DO, MS

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MAKING AN ACCURATE DIAGNOSIS: HOW TO USE THE IPF CONSENSUS GUIDELINES
Fernando J. Martinez, MD, MS

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SLEEP APNEA AND IPF: COINCIDENCE OR CAUSATION?
David Lederer, MD, MS

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PULMONARY HYPERTENSION IN PF: TO TEST? TO TREAT?

Steven M. Kawut, MD, MS

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GERD AND MICROASPIRATION IN PF: FUNDOPPLICATION FOR EVERYONE?

Joyce Lee, MD
QUESTIONS AND ANSWERS
LEADER: Leslie C. Watters, MD
All Clinical Session Faculty
LUNCH SESSION

CASE PRESENTATIONS WITH MASTER CLINICIANS

PANEL: Marvin I. Schwarz, MD; Steve D. Groshong, MD, PhD; Talmadge E. King, Jr., MD; David Lynch, MD; Ganesh Raghu, MD

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Jeffrey James Swigris, DO, MS

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EXISTING AND NEW TREATMENT OPTIONS: A GLOBAL PERSPECTIVE

LEADERS: Kevin K. Brown, MD; Christopher J. Ryerson, MD; Carlo Vancheri, MD

NON-PHARMACOLOGIC TREATMENT OPTIONS
Christopher J. Ryerson, MD

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EXISTING AND NEW TREATMENT OPTIONS: A GLOBAL PERSPECTIVE

PIRFENIDONE TREATMENT OF IPF IN THE EUROPEAN UNION

Carlo Vancheri, MD

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EXISTING AND NEW TREATMENT OPTIONS: A GLOBAL PERSPECTIVE

FUTURE OF THERAPIES AND CLINICAL TRIALS

Kevin K. Brown, MD

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CLINICAL TRIAL UPDATES (NOT CERTIFIED FOR CME)

LEADER: Kevin K. Brown, MD
Brad Maroni, MD, Biogen Idec; Claudio Pasquinelli, MD, PhD, Bristol-Myers Squibb; Gregory Ferguson, PhD, Celgene; Jack Stauffer, MD, FibroGen; Tom O’Riordan, MD, Gilead; Ari Gershman, DO, Genentech; David Wilkes, MD, ImmuneWorks; Jonathan Leff, MD, InterMune; Elizabeth Trehu, MD, Promedior

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EFFECTIVE ADVOCACY FOR PF
Brian Baird, MS, PhD

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## acronym glossary

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<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td>6MWD</td>
<td>six minute walk distance test</td>
</tr>
<tr>
<td>ABG</td>
<td>arterial blood gas</td>
</tr>
<tr>
<td>ACCP</td>
<td>American College of Chest Physicians</td>
</tr>
<tr>
<td>ADLs</td>
<td>activities of daily living</td>
</tr>
<tr>
<td>AIP</td>
<td>acute interstitial pneumonia</td>
</tr>
<tr>
<td>ALAT</td>
<td>Asociacion Latinoamericana de Torax</td>
</tr>
<tr>
<td>ARDS</td>
<td>acute respiratory distress syndrome</td>
</tr>
<tr>
<td>ATS</td>
<td>American Thoracic Society</td>
</tr>
<tr>
<td>BAL</td>
<td>bronchoalveolar lavage</td>
</tr>
<tr>
<td>BiPAP</td>
<td>bi-level positive airway pressure</td>
</tr>
<tr>
<td>BP</td>
<td>blood pressure</td>
</tr>
<tr>
<td>BX</td>
<td>biopsy</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers of Disease Control and Prevention</td>
</tr>
<tr>
<td>CF</td>
<td>cystic fibrosis</td>
</tr>
<tr>
<td>CHF</td>
<td>congestive heart failure</td>
</tr>
<tr>
<td>CLD</td>
<td>chronic lung disease</td>
</tr>
<tr>
<td>CMS</td>
<td>Center for Medicare and Medicaid Services</td>
</tr>
<tr>
<td>CO</td>
<td>carbon monoxide</td>
</tr>
<tr>
<td>CO₂</td>
<td>carbon dioxide</td>
</tr>
<tr>
<td>COP</td>
<td>cryptogenic organizing pneumonia</td>
</tr>
<tr>
<td>COPD</td>
<td>chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>CPAP</td>
<td>continuous positive airway pressure</td>
</tr>
<tr>
<td>CPR</td>
<td>cardiopulmonary resuscitation</td>
</tr>
<tr>
<td>CRT</td>
<td>Certified Respiratory Therapist</td>
</tr>
<tr>
<td>CT</td>
<td>CAT scan or computerized axial tomography</td>
</tr>
<tr>
<td>CTD-ILD</td>
<td>connective tissue associated interstitial lung disease</td>
</tr>
<tr>
<td>CXR</td>
<td>chest X-ray</td>
</tr>
<tr>
<td>DIP</td>
<td>desquamative interstitial pneumonia</td>
</tr>
<tr>
<td>DLCO</td>
<td>diffusing capacity of carbon monoxide</td>
</tr>
<tr>
<td>DNR</td>
<td>do not resuscitate</td>
</tr>
<tr>
<td>DOE</td>
<td>dyspnea on exertion</td>
</tr>
<tr>
<td>DPAP</td>
<td>demand positive airway pressure</td>
</tr>
<tr>
<td>DPLD</td>
<td>diffuse parenchymal lung disease</td>
</tr>
<tr>
<td>DX</td>
<td>diagnosis</td>
</tr>
<tr>
<td>ECG or EKG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>ECHO</td>
<td>echocardiogram</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>ERS</td>
<td>European Respiratory Society</td>
</tr>
<tr>
<td>ERV</td>
<td>expiratory reserve volume</td>
</tr>
<tr>
<td>ET</td>
<td>endotracheal tube</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FEF</td>
<td>forced expiratory flow</td>
</tr>
<tr>
<td>FEFMAX</td>
<td>forced expiratory flow at maximum effort</td>
</tr>
<tr>
<td>FEV</td>
<td>forced expiratory volume</td>
</tr>
<tr>
<td>FEV1</td>
<td>forced expiratory volume in 1 second</td>
</tr>
<tr>
<td>FIP</td>
<td>familial interstitial pneumonia</td>
</tr>
<tr>
<td>FPF</td>
<td>familial pulmonary fibrosis</td>
</tr>
<tr>
<td>FRC</td>
<td>functional residual capacity</td>
</tr>
<tr>
<td>FVC</td>
<td>forced vital capacity</td>
</tr>
<tr>
<td>GERD</td>
<td>gastroesophageal reflux disease</td>
</tr>
<tr>
<td>GI</td>
<td>gastrointestinal</td>
</tr>
<tr>
<td>GP</td>
<td>general practitioner</td>
</tr>
</tbody>
</table>
acronyms
acronym glossary

H
HEPA: high efficiency particulate air
HIPAA: Health Insurance Portability and Accountability Act
HP: hypersensitivity pneumonitis
HR: heart rate
HRCT: high resolution CT scan
HTN: hypertension

I
IADLs: instrumental activities of daily living
IC: inspiratory capacity
ICU: intensive care unit
IIP: idiopathic interstitial pneumonia
ILD: interstitial lung disease
IPF: idiopathic pulmonary fibrosis
IRV: inspiratory reserve volume

J
JRS: Japanese Respiratory Society

L
LIP: lymphocytic interstitial pneumonia
LOX: liquid oxygen
LPM: liters per minute oxygen or O₂ flow rate
LTC: long term care
LTX: lung transplant
LVRS: lung volume reduction surgery

M
MCS: multiple chemical sensitivities
MDI: metered dose inhaler
MRI: magnetic resonance imaging
MVV: maximal voluntary ventilation

N
NHLBI: National Heart, Lung, and Blood Institute
NICE: National Institute for Health and Care Excellence (UK)
NIH: National Institutes of Health
NIV: non-invasive ventilator
NSIP: non-specific interstitial pneumonia

O
O₂: oxygen
OAD: obstructive airway disease
OLD: occupational lung disease
OSA: obstructive sleep apnea
OTC: over the counter

P
PaO₂: partial pressure of oxygen in arterial blood
PAP: positive airway pressure
PCO₂: partial pressure of carbon dioxide in arterial blood
PCP: primary care physician
PE: pulmonary embolism or pulmonary edema
PEEP: positive end expiratory pressure
PEFR: peak expiratory flow rate
PEP: positive expiratory pressure
PF-CVD: pulmonary fibrosis associated with a collagen vascular disorder
PF: pulmonary fibrosis
PFT: pulmonary function test
PH: pulmonary hypertension
PLB: pursed lip breathing
PND: paroxysmal nocturnal dyspnea/post nasal drip
PO₂: oxygen tension in arterial blood
POLST: Physician Orders for Life-Sustaining Treatment
PPH: primary pulmonary hypertension
PPV: positive pressure ventilation
PR: pulmonary rehabilitation
PT: physical therapy
PTX: pneumothorax
PULM OR PULMO: pulmonary
acronyms
acronym glossary

Q
QOL: quality of life

R
R/O: rule out
RA: rheumatoid arthritis
RAD: reactive airway disease
RB-ILD: respiratory bronchiolitis associated interstitial lung disease
RCT: randomized controlled trial
RDS: respiratory distress syndrome
RLD: restrictive lung disease
RLS: restless leg syndrome
RR: respiratory rate
RRT: Registered Respiratory Therapist
RT: Respiratory Therapist/respiratory therapy
RV: residual volume
Rx: treatment/therapy/prescription

S
SaO₂: arterial blood oxygen saturation
SOB: shortness of breath
SSDI: Social Security Disability Insurance
SSI: Supplemental Security Insurance

T
TLC: total lung capacity
TTO₂: transtracheal oxygen
TV: tidal volume
TX: transplant

U
UIP: usual interstitial pneumonia
URI: upper respiratory infection

V
VATS: video assisted thoracic surgery
VC: vital capacity
VCO₂: carbon dioxide production
VO₂: oxygen consumption
VQ SCAN: ventilation perfusion scan