PFF

SUMMIT

FROM BENCH
TO BEDSIDE

2015

WASHINGTON DC
NOVEMBER 12–14

PRESENTED BY

Pulmonary Fibrosis
FOUNDATION

welcome
letter from our cmo

PFF
SUMMIT 2015
FROM BENCH
TO BEDSIDE

Dear Friends of the Foundation,

Welcome to the *PFF Summit 2015: From Bench to Bedside*. This is our third biennial scientific health care conference on pulmonary fibrosis (PF), the largest of its kind in the world. The previous *Summits* in 2011 and 2013 were highly successful and created many new opportunities for international collaborations, enabling us to provide important information and support to patients, and assisting clinicians and researchers from around the world to make meaningful connections with one another. We hope that the upcoming *Summit* will serve as a catalyst for advancements in diagnosis and care and help stimulate the research needed to find new treatments — and ultimately, a cure — for this disease.

After the *PFF Summit 2013*, many of you told us that you appreciated being able to interact with attendees from the entire PF community. This year, we are pleased to announce an addition to our programming specifically aimed at increasing these interactions. **Each day of the conference, a keynote address and plenary session will bring patients, caregivers, and health care professionals together in one room.** We are pleased to present two outstanding keynote speakers this year: Pat Furlong, the founding President and CEO of Parent Project Muscular Dystrophy (PPMD), and Janet Woodcock, MD, Director of the FDA's Center for Drug Evaluation and Research (CDER).

Many people have worked hard to organize the *PFF Summit 2015*. I would like to thank members of the *Summit* Organizing Committee and the Foundation's staff. I would also like to thank our sponsors, whose generosity makes the *Summit* possible. It is because of their support that we are able to offer lower registration rates to health care professionals and deeply discounted rates to the patient and caregiver community. I am also grateful to this year's outstanding international faculty, whose insights will greatly contribute to the success of this conference. Last but not least, I would like to thank the patient community, whose members serve as the inspiration for everything we do at the PFF.

Warmest Regards,

GREGORY P. COSGROVE, MD, FCCP
CHIEF MEDICAL OFFICER
PULMONARY FIBROSIS FOUNDATION

welcome
letter from the summit chair

PFF
SUMMIT
FROM BENCH 2015
TO BEDSIDE

Dear Summit Participants,

On behalf of the Pulmonary Fibrosis Foundation (PFF) leadership and the conference organizing committee, it is my pleasure to welcome you to the *PFF Summit 2015: From Bench to Bedside*. The primary goal of this biennial conference has always been to provide a forum for patients, providers, researchers, and other stakeholders to interact around the topic of pulmonary fibrosis (PF). We strongly believe that improving the lives of patients who suffer from PF is best served through patient-centered, collaborative efforts, and we are thrilled to see so many of you in Washington, DC, participating this year.

The PFF held its first *Summit* in 2011 to encourage interaction among stakeholders, expand our collective knowledge, and foster progress in the field of PF. This year marks the third *Summit* event, and we have invited a diverse and distinguished faculty from around the world to participate. One highlight of the *PFF Summit 2015* is the inclusion of two plenary sessions open to all attendees that will feature keynote presentations and panel discussions on the future of drug development and collaborative research in PF. In addition, there are sessions designed specifically for patients that review recent advances in the management of PF, and scientific sessions that highlight cutting edge basic, translational, and clinical science.

I hope you find this year's *Summit* both educational and motivational — combining new learning with new relationships that push you to renew your commitment to cure PF. Your engagement and input during the meeting will help shape the future of PF care and research. Thank you all for attending and participating!

Sincerely,

HAROLD R. COLLARD, MD
CHAIR, PFF SUMMIT 2015

welcome
what's inside

PFF
SUMMIT
FROM BENCH 2015
TO BEDSIDE

what's inside

about the Pulmonary Fibrosis Foundation

OUR MISSION AND VISION

The Pulmonary Fibrosis Foundation (PFF) is focused on our mission to serve as the trusted resource for the pulmonary fibrosis (PF) community by raising awareness, providing disease education, and funding research. The Foundation imagines a world without pulmonary fibrosis. We aim to achieve this vision by offering programs that engage the PF community and help advance research that one day will achieve a cure.

PROGRAMS AND INITIATIVES

Our programs and initiatives include:

GLOBAL PULMONARY FIBROSIS AWARENESS MONTH

The PF community unites during Global Pulmonary Fibrosis Awareness Month in September as a collective voice to enhance disease awareness and provide outreach to those in need. To learn how to participate, visit www.globalPFawareness.org.

PFF AMBASSADOR PROGRAM

The PFF Ambassador program empowers patients, caregivers, and health care professionals as spokespersons for the PF community on behalf of the PFF. PFF Ambassadors promote disease awareness, provide up-to-date information, and offer hope and inspiration to those affected by pulmonary fibrosis. PFF Ambassadors are available to speak at PFF Care Center Network events, support group meetings, fundraising events, and other disease awareness programs.

PFF CARE CENTER NETWORK

The PFF Care Center Network (CCN) is a growing group of medical centers with proven expertise in treating patients with fibrotic lung diseases and are dedicated to offering high quality care to those living with these diseases. By sharing knowledge of pulmonary fibrosis, the CCN is elevating the standard of care for PF patients. More information about the CCN is available on page 9.

PFF DISEASE EDUCATION WEBINAR SERIES

The PFF Disease Education Webinar Series engages the PF community in an online webinar discussion, where they learn from, connect with, and pose questions to leading pulmonary fibrosis specialists each month.

PROGRAMS AND INITIATIVES (continued)

PFF PATIENT COMMUNICATION CENTER

The PFF Patient Communication Center (PCC) offers the most up-to-date medical information, communicates where and how to access support services, and provides information about other essential resources important to patients, caregivers, and health care providers. Call 844.TalkPFF (844.825.5733) or email pcc@pulmonaryfibrosis.org to speak with someone today.

PFF SUMMIT: FROM BENCH TO BEDSIDE

The PFF's biennial scientific conference is a unique forum that brings together a multifaceted group of physicians, researchers, allied health professionals, industry representatives, patients, and caregivers. *PFF Summit* participants engage in networking functions, educational presentations, panel discussions, and poster presentations. Get involved with the *PFF Summit 2017* by considering a sponsorship. Visit **www.pffsummit.org** for more information.

PFF SUPPORT GROUP LEADER NETWORK

The PFF Support Group Leader Network provides a forum for PF support group leaders to connect, exchange ideas, and share best practices. The Leanne Storch Support Group Fund further enhances the support group experience and assists the needs of the Network by funding educational events, helping establish new groups, and supporting related activities.

TEAM PFF

Each year *Team PFF* members take action by leading fundraising events in honor of a loved one. *Team PFF* hosts more than 100 events annually to support disease awareness and research. Learn how to organize your own *Team PFF* event or support a *Team PFF* event in your area: **www.pulmonaryfibrosis.org/teampff** or email teampff@pulmonaryfibrosis.org.

PFF MEDICAL ADVISORY BOARD

Our Medical Advisory Board (MAB) is comprised of recognized experts in pulmonary medicine from leading academic and medical institutions around the world. The MAB and the biennial *PFF Summit* provide forums in which the Foundation maintains an ongoing dialogue with physicians, researchers, industry representatives, and the patient community. This collaborative environment helps the Foundation achieve many of our goals.

Our peer-reviewed research program provides monetary awards to scientific initiatives that improve the understanding of pulmonary fibrosis, as well as those that will lead to successful therapies and ultimately a cure. We have developed significant relationships with industry partners and upheld our position as the honest broker to inform those affected by pulmonary fibrosis of important scientific breakthroughs.

about the foundation
pff care center network and pff patient registry

PFF
SUMMIT
FROM BENCH 2015
TO BEDSIDE

09

ccn and patient registry

THE PFF CARE CENTER NETWORK AND THE PFF PATIENT REGISTRY

The PFF Care Center Network (CCN) is comprised of medical centers with expertise in treating pulmonary fibrosis (PF), a group of lung disorders that are often difficult to diagnose and manage. The CCN uses a multidisciplinary approach to deliver comprehensive patient care, forming multi-specialized care teams comprised of experts in interstitial lung disease in pulmonary medicine, rheumatology, radiology, and pathology. This multidisciplinary approach is critical to managing a complex disease like PF and ensuring patients receive an accurate diagnosis, obtain quality clinical care, and acquire important support services. The care teams at CCN centers are also involved in research to improve care and discover new treatments for PF.

The PFF Patient Registry is a collaborative effort that brings together multiple stake-holders whose aim is to advance research and improve the quality of life of patients with PF. The Registry is unique as it is the only existing registry that includes data on pulmonary fibrosis from all causes, not just idiopathic pulmonary fibrosis.

The CCN and Registry are related and enhance each other. The CCN provides the infrastructure to execute Registry activities. All data entered into the Registry will come through a CCN site. The CCN promotes high-quality, comprehensive patient care, and ensures standard data collection procedures and controls for maximum data integrity. The CCN's broader goal is to improve the quality of life for patients with PF. The CCN and Registry will work in tandem to address complex problems related to fibrotic lung disorders.

PFF PATIENT REGISTRY

PFF CARE CENTER NETWORK

Pulmonary Fibrosis
FOUNDATION

pff research fund

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 Junior Investigator Awards:** These awards of up to $50,000, given over a two-year period, encourage junior 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:** These unique partnerships allow the PFF, in collaboration with leading lung health organizations, to jointly award grants focusing on PF.

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/medical-community/pff-research-funds

our history and people

HISTORY OF THE FOUNDATION

Founded in 2000 by brothers Albert Rose and Michael Rosenzweig, PhD, the Pulmonary Fibrosis Foundation is a 501(c)(3) nonprofit organization dedicated to identifying effective PF treatments and assisting those living with the disease. The brothers experienced firsthand the devastating effects of PF when their sister Claire passed away from the disease. Both brothers were also diagnosed with PF, and it was their vision and dedication that led to the creation of the Pulmonary Fibrosis Foundation.

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*Scientific Advisory Committee

LET THE WORLD KNOW

global
PULMONARY
FIBROSIS
awareness
month
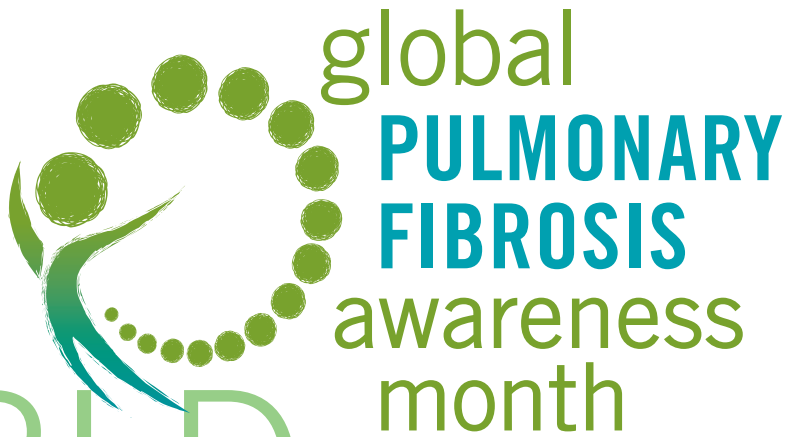
SEPTEMBER 2016

www.globalPFawareness.org

save the date!

NOVEMBER 9–11, 2017

PFF SUMMIT

FROM BENCH 2017
TO BEDSIDE

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

Visit the voting station by the Registration and Information Desk to cast your vote.

Your choices are:
    PHOENIX, AZ
    HOUSTON, TX
    MIAMI, FL
    ATLANTA, GA
    CHICAGO, IL

To receive information about the *PFF Summit 2017*, please email summit@pulmonaryfibrosis.org or call 888.733.6741.

meeting info and space map(s)
meeting information and procedures

PFF
SUMMIT 2015
FROM BENCH
TO BEDSIDE

15

meeting information and procedures

ACCREDITATION AND DESIGNATION STATEMENTS

Accreditation and designation information can be found on page 35.

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 HALL, POSTER HALL, AND MEALS

You must have a name badge to enter the sessions, Exhibit Hall, Poster Hall and to participate in the Welcome Reception, Networking Dinner, and meal functions. The Exhibit Hall and Poster Hall are open during the following hours:

Thursday, November 12 5:00 p.m.–8:00 p.m.
Friday, November 13 7:00 a.m.–5:45 p.m.
Saturday, November 14 7:00 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.

COMMUNITY MAP AND SOCIAL MEDIA SCREENS

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.

Social media screens will display messages from anyone using the hashtag #PFFSummit2015.

INTERACTIVE POSTER DISPLAY

Learn about important PF research by visiting our interactive poster display to view all the posters from the Thursday Poster Presentation. The interactive poster display is situated by the entrance to the Grand Ballroom.

OXYGEN STATION

Oxygen refills will be available during *Summit* hours on Thursday, November 12, Friday, November 13, and Saturday, November 14, to patients with valid prescriptions and who have made a request in advance.

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 2015

The *PFF Summit 2015* will be photographed, videotaped, and/or recorded in its entirety by staff and third-party vendors. All sessions will be available post-conference via, but not limited to, the Pulmonary Fibrosis Foundation and *PFF Summit* 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, email, and social media. Those who do not wish to be filmed or photographed may ask a PFF staff member for an orange lanyard at the Registration and Information Desk 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 The France Foundation present this information for educational purposes only. The content is provided solely by faculty members who have been selected because of recognized expertise in their fields. 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 The France Foundation assume no liability for the information herein.

POST-SUMMIT SURVEY

After the meeting, you will receive a request to take a survey regarding your experience at the *Summit*.

QUESTIONS OR ASSISTANCE

If you have any questions or need assistance, please visit the Registration and Information Desk.

meeting info and space map(s)
navigating the summit

PFF
SUMMIT 2015
FROM BENCH
TO BEDSIDE

17

OVERVIEW (A–Z)

The *PFF Summit 2015* activities take place on three different levels of the JW Marriott Washington, DC.
All patient and caregiver sessions take place in the Capitol Ballroom on the lower level. The sessions for health care professionals, as well as the plenary sessions, take place in the Grand Ballroom, also on the lower level.

ADVOCACY WORKSHOP; SURVEY SESSION
(SIGN-UP ONLY)
`MEZZ` HART and CANNON

BOARD OF DIRECTORS ANNUAL MEETING
`LOBBY` CONGRESSIONAL

BOEHRINGER INGELHEIM MEETING SUITE
`MEZZ` COMMERCE

EXHIBIT HALL
`LOWER` CAPITOL FOYER and GRAND BALLROOM, SALON IV

GENENTECH MEETING SUITE
`MEZZ` STATE

HEALTH CARE PROFESSIONAL SESSIONS
`LOWER` GRAND BALLROOM, SALONS I, II, and III

NETWORKING DINNER
`LOWER` GRAND BALLROOM, SALONS I, II, and III

OXYGEN STATION
`LOWER` by the GRAND OFFICE

PATIENT AND CAREGIVER SESSIONS
`LOWER` CAPITOL BALLROOM, SALONS D, E, F, and G

PFF CARE CENTER NETWORK AND PFF PATIENT
REGISTRY MEETING
`LOWER` GRAND BALLROOM, SALONS I and II

PFF STAFF OFFICE
`LOWER` CAPITOL OFFICE (behind REGISTRATION)

PLENARY SESSIONS
`LOWER` GRAND BALLROOM, SALONS I, II, and III

POSTER HALL
`LOBBY` PENN AVENUE TERRACE

REGISTRATION AND INFORMATION DESK
`LOWER` by the CAPITOL OFFICE

RESEARCH ADVISORY FORUM (RAF)
`LOBBY` CONGRESSIONAL

SPEAKER READY ROOM
(FACULTY, PFF STAFF, AND AV ONLY)
`LOWER` INDEPENDENCE

SUPPORT GROUP LEADER NETWORK MEETING
`LOWER` CAPITOL BALLROOM, SALONS D and E

TEAM PFF MEETING
`LOBBY` SENATE

WELCOME BAG PICKUP
`LOWER` GRAND BALLROOM, SALON IV

WELCOME RECEPTION AND POSTER
PRESENTATIONS
`LOBBY` PENN AVENUE TERRACE

LEVELS

meeting info and space map(s)

LOBBY LEVEL

STARBUCKS

TO SELF-PARKING
& FOOD COURT

SENATE
A

CONGRESSIONAL
B **C**

ESCALATORS TO
PENNSYLVANIA
AVENUE

ELEVATORS

GIFT SHOP

ATRIUM

EXECUTIVE
OFFICES

FRONT DESK

LOBBY

A

STAIRS TO
PENNSYLVANIA
AVENUE

STAIRS UP

CONCIERGE

BELL
STAND

1 **2**

**PENN AVENUE
TERRACE**

14TH STREET
ENTRANCE

B

LOBBY

1 WELCOME RECEPTION
AND POSTER PRESENTATIONS
PENN AVENUE TERRACE

2 POSTER HALL
PENN AVENUE TERRACE

ANCILLARY MEETINGS

A TEAM PFF MEETING
SENATE

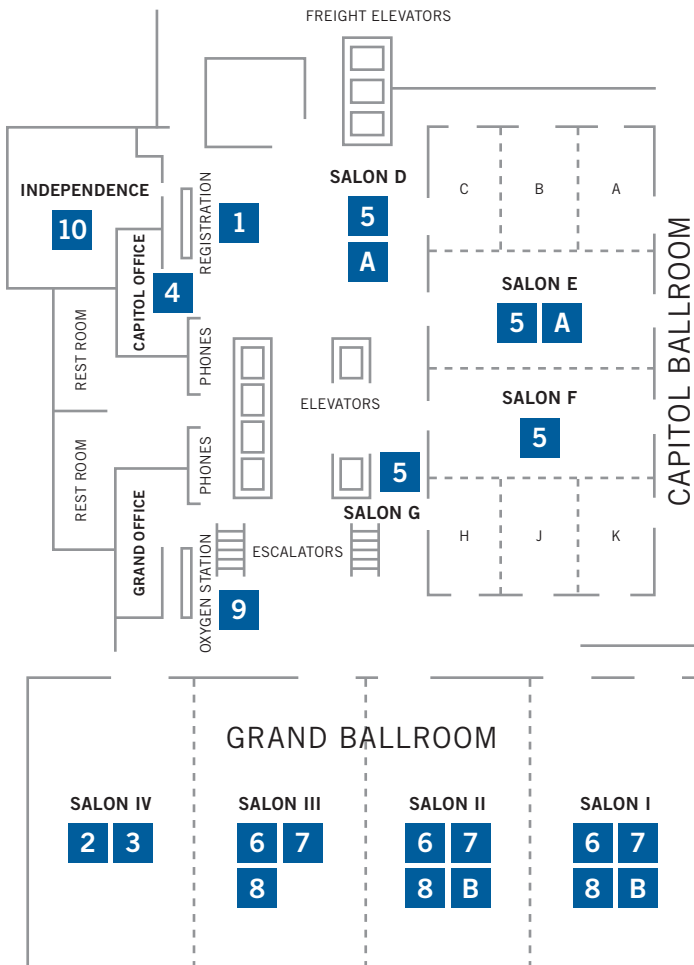**B** BOARD OF DIRECTORS
ANNUAL MEETING
CONGRESSIONAL

C RESEARCH ADVISORY
FORUM (RAF)
CONGRESSIONAL

LOWER LEVEL

LOWER

1 **REGISTRATION AND INFORMATION DESK**
by the CAPITOL OFFICE

2 **EXHIBIT HALL**
GRAND BALLROOM, SALON IV

3 **WELCOME BAG PICKUP**
GRAND BALLROOM, SALON IV

4 **PFF STAFF OFFICE**
CAPITOL OFFICE (behind REGISTRATION)

5 **PATIENT AND CAREGIVER SESSIONS**
CAPITOL BALLROOM, SALONS D, E, F, and G

6 **HEALTH CARE PROFESSIONAL SESSIONS**
GRAND BALLROOM, SALONS I, II, and III

7 **PLENARY SESSIONS**
GRAND BALLROOM, SALONS I, II, and III

8 **NETWORKING DINNER**
GRAND BALLROOM, SALONS I, II, and III

9 **OXYGEN STATION**
by the GRAND OFFICE

10 **SPEAKER READY ROOM**
(FACULTY, PFF STAFF, AND AV ONLY)
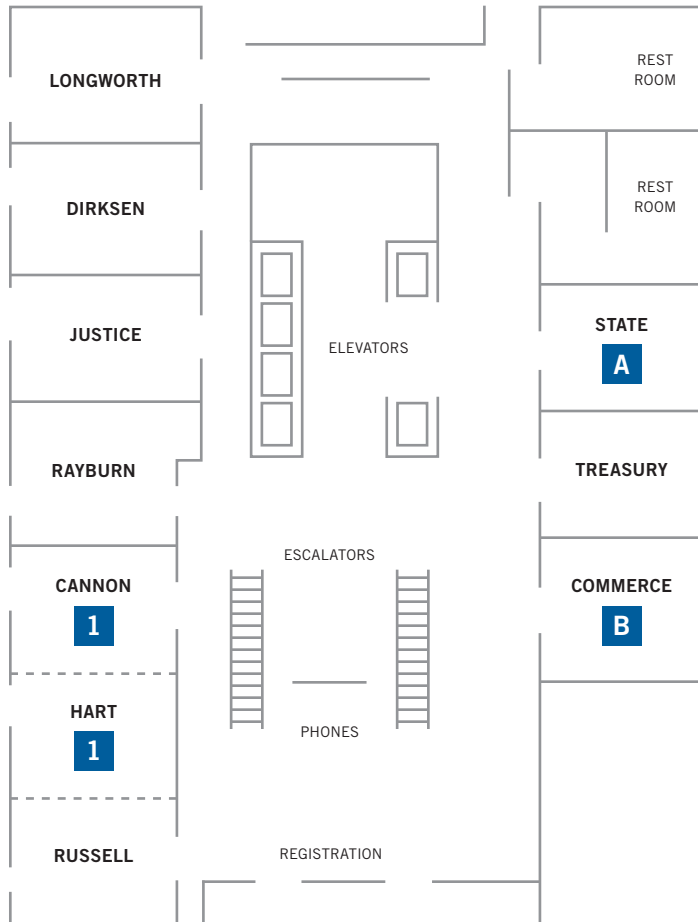INDEPENDENCE

ANCILLARY MEETINGS

A **SUPPORT GROUP LEADER NETWORK MEETING**
CAPITOL BALLROOM, SALONS D and E

B **PFF CARE CENTER NETWORK AND PFF PATIENT REGISTRY MEETING**
GRAND BALLROOM, SALONS I and II

MEZZANINE LEVEL

MEZZ

1 **ADVOCACY WORKSHOP; SURVEY SESSION (SIGN-UP ONLY)**
HART and CANNON

ANCILLARY MEETINGS

A **GENENTECH MEETING SUITE**
STATE

B **BOEHRINGER INGELHEIM MEETING SUITE**
COMMERCE

thursday > welcome

11:00 a.m.–8:00 p.m.	**REGISTRATION**
3:00 p.m.–5:00 p.m.	**POSTER SET-UP**
5:00 p.m.–8:00 p.m.	**WELCOME RECEPTION AND POSTER PRESENTATION**

thursday > pre-conference interactive session for patients and caregivers

TAKING CARE OF YOURSELF: SHARED HEALTHCARE DECISION-MAKING

1:00 p.m.–1:15 p.m.	**WELCOME AND OVERVIEW** Harold R. Collard, MD; Kathleen O. Lindell, PhD, RN
1:15 p.m.–2:00 p.m.	**PATIENT AND CAREGIVER PULMONARY REHABILITATION WORKSHOP** Chris D. Schumann, MS, CES, RCEP
2:00 p.m.–2:45 p.m.	**OXYGEN THERAPY WORKSHOP** Susan S. Jacobs, RN, MS
2:45 p.m.–3:00 p.m.	**BREAK**
3:00 p.m.–4:00 p.m.	**PATIENT BREAKOUT SESSION — PROVIDING PSYCHOSOCIAL SUPPORT** Deborah Gillman, PhD
3:00 p.m.–4:00 p.m.	**CAREGIVER BREAKOUT SESSION — PROVIDING PSYCHOSOCIAL SUPPORT** Jane Harrison, LCSW, CCTSW

friday > sessions

7:00 a.m.–8:15 a.m.	**REGISTRATION AND CONTINENTAL BREAKFAST**
8:15 a.m.–8:30 a.m.	**WELCOME AND INTRODUCTION** Harold R. Collard, MD; Gregory P. Cosgrove, MD, FCCP
8:30 a.m.–9:00 a.m.	**KEYNOTE ADDRESS:** **THE FUTURE OF DRUG DEVELOPMENT IN PULMONARY FIBROSIS —** **A REGULATORY PERSPECTIVE** Janet Woodcock, MD
9:00 a.m.–10:00 a.m.	**PLENARY SESSION AND PANEL DISCUSSION:** **THE FUTURE OF CLINICAL TRIALS IN PULMONARY FIBROSIS** **LEADERS:** David J. Lederer, MD, MS; Kevin K. Brown, MD **PANEL:** Williamson Bradford, MD, PhD; A. Bruce Montgomery, MD; Fernando J. Martinez, MD, MS; Janet Woodcock, MD; R. Bruce Snyder; Doug Jones
10:00 a.m.–10:30 a.m.	**BREAK / VISIT EXHIBITS**

PULMONARY FIBROSIS: WHAT AND WHY

LEADERS: Joao Alberto M. de Andrade, MD; Joyce Lee, MD

10:30 a.m.–10:35 a.m.	**WELCOME, OVERVIEW OF P/C SESSIONS — HOUSEKEEPING** Harold R. Collard, MD
10:35 a.m.–10:40 a.m.	**SESSION LEADER INTRODUCTION** Joyce Lee, MD
10:40 a.m.–11:10 a.m.	**WHAT IS PULMONARY FIBROSIS AND WHY IS IT A PROBLEM?** Joyce Lee, MD
11:10 a.m.–11:40 a.m.	**DIAGNOSING THE CAUSE OF PULMONARY FIBROSIS** Kevin F. Gibson, MD
11:40 a.m.–12:00 p.m.	**COMMUNICATING PROGNOSIS AND GOALS OF CARE** Sonye K. Danoff, MD, PhD
12:00 p.m.–12:15 p.m.	**QUESTION-AND-ANSWER PERIOD AND PANEL DISCUSSION** **LEADER:** Joao Alberto M. de Andrade, MD

friday > sessions

12:15 p.m.–1:15 p.m.	**PULMONARY FIBROSIS ADVOCACY WORKSHOP**
	You must have pre-registered and have a name badge to enter the session. The session will be held in the Cannon-Hart meeting room on the Mezzanine Level. Lunch will be provided at the meeting.
12:15 p.m.–1:15 p.m.	**LUNCH / NETWORKING / VISIT EXHIBITS / ADVOCACY BREAKOUTS**

PULMONARY FIBROSIS MANAGEMENT STRATEGIES I

LEADERS: Marilyn K. Glassberg, MD; Chris D. Schumann, MS, CES, RCEP; Rafael L. Perez, MD

1:15 p.m.–1:20 p.m.	**SESSION LEADER INTRODUCTION**
	Chris D. Schumann, MS, CES, RCEP
1:20 p.m.–1:35 p.m.	**PATIENT PERSPECTIVE: LIVING WELL WITH PULMONARY FIBROSIS**
	Pete Mulliner
1:35 p.m.–1:55 p.m.	**PHARMACOLOGIC THERAPY**
	Charlene D. Fell, MD, MSc
1:55 p.m.–2:15 p.m.	**PULMONARY REHABILITATION AND OXYGEN THERAPY**
	Anne E. Holland, PhD
2:15 p.m.–2:35 p.m.	**MANAGING COMORBIDITY**
	Vincent Cottin, MD, PhD
2:35 p.m.–2:45 p.m.	**QUESTION-AND-ANSWER PERIOD AND PANEL DISCUSSION**
	LEADER: Marilyn K. Glassberg, MD
6:30 p.m.–7:30 p.m.	**COCKTAIL HOUR**
7:30 p.m.–10:00 p.m.	**NETWORKING DINNER**

saturday > sessions

7:00 a.m.–8:15 a.m.	**REGISTRATION AND CONTINENTAL BREAKFAST**
8:15 a.m.–8:30 a.m.	**WELCOME AND INTRODUCTION** Harold R. Collard, MD; Gregory P. Cosgrove, MD, FCCP
8:30 a.m.–9:00 a.m.	**KEYNOTE SPEAKER:** **COLLABORATIVE NETWORKS AS TOOLS FOR IMPROVING CLINICAL CARE** Pat Furlong
9:00 a.m.–10:00 a.m.	**PLENARY SESSION AND PANEL DISCUSSION:** **LEVERAGING THE PFF CARE CENTER NETWORK** **LEADERS:** Vincent Cottin, MD, PhD; Kevin R. Flaherty, MD, MS; Jesse Roman, MD **PANEL:** Jerry Eu, MD; Pat Furlong; Dave Sherry; John Morthanos
10:00 a.m.–10:30 a.m.	**BREAK / VISIT EXHIBITS**

PULMONARY FIBROSIS MANAGEMENT STRATEGIES II: PLANNING FOR THE FUTURE

LEADERS: Kathleen O. Lindell, PhD, RN; Timothy P. W. Whelan, MD

10:30 a.m.–10:35 a.m.	**INTRODUCTION AND HOUSEKEEPING**
10:35 a.m.–10:40 a.m.	**SESSION LEADER INTRODUCTION** Timothy P. W. Whelan, MD
10:40 a.m.–11:00 a.m.	**LUNG TRANSPLANTATION** Steven D. Nathan, MD, FCCP
11:00 a.m.–11:20 a.m.	**SYMPTOM MANAGEMENT** Maryl E. Kreider, MD, MSCE
11:20 a.m.–12:00 p.m.	**PALLIATIVE AND ADVANCED CARE** Susan S. Jacobs, RN, MS
12:00 p.m.–12:15 p.m.	**QUESTION-AND-ANSWER PERIOD AND PANEL DISCUSSION** **LEADER:** Kathleen O. Lindell, PhD, RN

saturday > sessions

12:15 p.m.–1:15 p.m.	**PULMONARY FIBROSIS SURVEY SESSION**

You must have pre-registered and have a name badge to enter the session. The session will be held in the Cannon-Hart meeting room on the Mezzanine Level. Lunch will be provided at the meeting.

12:15 p.m.–1:15 p.m.	**LUNCH / NETWORKING / VISIT EXHIBITS / ADVOCACY BREAKOUTS**

PATIENT-CENTERED RESEARCH IN PULMONARY FIBROSIS

LEADERS: Joseph A. Lasky, MD; Amy Hajari Case, MD

1:15 p.m.–1:20 p.m.	**SESSION LEADER INTRODUCTION** Amy Hajari Case, MD
1:20 p.m.–1:35 p.m.	**PATIENT PERSPECTIVE: LIVING WELL WITH PULMONARY FIBROSIS** Charolette Saunders
1:35 p.m.–1:55 p.m.	**PFF PATIENT SURVEY RESULTS** Gregory P. Cosgrove, MD, FCCP
1:55 p.m.–2:15 p.m.	**THE PROMISE OF REGISTRIES** Christopher J. Ryerson, MD
2:15 p.m.–2:35 p.m.	**CLINICAL TRIALS IN THE ERA OF EFFECTIVE THERAPIES** Luca Richeldi, MD, PhD
2:35 p.m.–2:50 p.m.	**QUESTION-AND-ANSWER PERIOD AND PANEL DISCUSSION** **LEADER:** Joseph A. Lasky, MD
2:50 p.m.–3:00 p.m.	**CLOSING REMARKS** Gregory P. Cosgrove, MD, FCCP

agenda > health care professionals
thursday > welcome + friday > scientific sessions

PFF
SUMMIT 2015
FROM BENCH
TO BEDSIDE

27

thursday > welcome

11:00 a.m.–8:00 p.m.	**REGISTRATION**
3:00 p.m.–5:00 p.m.	**POSTER SET-UP**
5:00 p.m.–8:00 p.m.	**WELCOME RECEPTION AND POSTER PRESENTATION**

friday > scientific sessions

7:00 a.m.–8:15 a.m.	**REGISTRATION AND CONTINENTAL BREAKFAST**
8:15 a.m.–8:30 a.m.	**WELCOME AND INTRODUCTION**
	Harold R. Collard, MD; Gregory P. Cosgrove, MD, FCCP
8:30 a.m.–9:00 a.m.	**KEYNOTE ADDRESS:**
	THE FUTURE OF DRUG DEVELOPMENT IN PULMONARY FIBROSIS — A REGULATORY PERSPECTIVE
	Janet Woodcock, MD
9:00 a.m.–10:00 a.m.	**PLENARY SESSION AND PANEL DISCUSSION:**
	THE FUTURE OF CLINICAL TRIALS IN PULMONARY FIBROSIS
	LEADERS: David J. Lederer, MD, MS; Kevin K. Brown, MD
	PANEL: Williamson Bradford, MD, PhD; A. Bruce Montgomery, MD; Fernando J. Martinez, MD, MS; Janet Woodcock, MD; R. Bruce Snyder; Doug Jones
10:00 a.m.–10:30 a.m.	**BREAK / VISIT EXHIBITS**
10:30 a.m.–10:45 a.m.	**POSTER AWARDEE PRESENTATION I**
	Poster awardee — TBD by committee during Poster Presentation on Thursday, November 12

friday > scientific sessions

TRANSLATIONAL SCIENCE: PROGRESS TOWARDS PERSONALIZED MEDICINE FOR IPF — BIG DATA MEETS PATIENT CARE

LEADERS: Ivan O. Rosas, MD; Christine Kim Garcia, MD, PhD

Time	Session
10:45 a.m.–11:00 a.m.	**AN OVERVIEW OF PERSONALIZED MEDICINE FOR PULMONARY FIBROSIS** Ivan O. Rosas, MD
11:00 a.m.–11:20 a.m.	**GENETICS OF PULMONARY FIBROSIS** Christine Kim Garcia, MD, PhD
11:20 a.m.–11:40 a.m.	**MOLECULAR AND CELLULAR BIOMARKERS OF PULMONARY FIBROSIS** Naftali Kaminski, MD
11:40 a.m.–12:00 p.m.	**INTEGRATING BIOMARKERS IN CLINICAL STUDIES TO AFFECT PATIENT CARE** Fernando J. Martinez, MD, MS
12:00 p.m.–12:15 p.m.	**QUESTION-AND-ANSWER PERIOD AND PANEL DISCUSSION** **LEADERS:** Ivan O. Rosas, MD; Christine Kim Garcia, MD, PhD
12:15 p.m.–1:15 p.m.	**PULMONARY FIBROSIS ADVOCACY WORKSHOP** You must have pre-registered and have a name badge to enter the session. The session will be held in the Cannon-Hart meeting room on the Mezzanine Level. Lunch will be provided at the meeting.
12:15 p.m.–1:15 p.m.	**LUNCH / NETWORKING / VISIT EXHIBITS / ADVOCACY BREAKOUTS**
1:15 p.m.–1:30 p.m.	**POSTER AWARDEE PRESENTATION II** Poster awardee — TBD by committee during Poster Presentation on Thursday, November 12

agenda > health care professionals
friday > scientific sessions

PFF
SUMMIT 2015
FROM BENCH
TO BEDSIDE

29

friday > scientific sessions

BASIC SCIENCE: LUNG REMODELING AND REGENERATION

LEADERS: Andrew M. Tager, MD; Erica L. Herzog, MD, PhD

1:30 p.m.–1:35 p.m.	**SESSION LEADER II INTRODUCTION** Erica L. Herzog, MD, PhD
1:35 p.m.–1:55 p.m.	**FIBROSIS AS A DISEASE OF AGING AND MITOCHONDRIAL DYSFUNCTION** Ana L. Mora, MD
1:55 p.m.–2:15 p.m.	**MECHANOTRANSDUCTION AND THE ROLE OF TISSUE STIFFNESS IN FIBROSIS** Mitchell A. Olman, MD, MA
2:15 p.m.–2:35 p.m.	**THE ROLE OF MACROPHAGES IN FIBROSIS** A. Michael R. Blackburn, MD, PhD
2:35 p.m.–2:45 p.m.	**DISCUSSION, SESSION OVERVIEW, AND CLOSE** Andrew M. Tager, MD
2:45 p.m.–3:15 p.m.	**BREAK / VISIT EXHIBITS**
3:15 p.m.–3:30 p.m.	**POSTER AWARDEE PRESENTATION III** Poster awardee—TBD by committee during Poster Presentation on Thursday, November 12

friday > scientific sessions

CLINICAL SCIENCE: PATIENT-CENTERED ENDPOINTS — SYMPTOMS AND FUNCTIONAL STATUS

LEADERS: Rafael L. Perez, MD; Sonye K. Danoff, MD, PhD

Time	Session
3:30 p.m.–3:35 p.m.	**SESSION LEADER III INTRODUCTION** Sonye K. Danoff, MD, PhD
3:35 p.m.–3:55 p.m.	**HOW TO BUILD A PATIENT-REPORTED OUTCOME (PRO)** Hilary Wilson, PhD
3:55 p.m.–4:15 p.m.	**MEASURING FUNCTION: BEYOND THE 6MWT** Amy L. Olson, MD, MSPH
4:15 p.m.–4:35 p.m.	**PATIENT-CENTERED RESEARCH: PCORI AND THE PATIENT VOICE** Sonye K. Danoff, MD, PhD
4:35 p.m.–4:40 p.m.	**PANEL DISCUSSION**
4:40 p.m.–4:45 p.m.	**SESSION CLOSING REMARKS** Sonye K. Danoff, MD, PhD; Rafael L. Perez, MD
6:30 p.m.–7:30 p.m.	**COCKTAIL HOUR**
7:30 p.m.–10:00 p.m.	**NETWORKING DINNER**

saturday > clinical sessions

7:00 a.m.–8:15 a.m.	**REGISTRATION AND CONTINENTAL BREAKFAST**
8:15 a.m.–8:30 a.m.	**WELCOME AND INTRODUCTION** Harold R. Collard, MD; Gregory P. Cosgrove, MD, FCCP
8:30 a.m.–9:00 a.m.	**KEYNOTE SPEAKER:** **COLLABORATIVE NETWORKS AS TOOLS FOR IMPROVING CLINICAL CARE** Pat Furlong
9:00 a.m.–10:00 a.m.	**PLENARY SESSION AND PANEL DISCUSSION:** **LEVERAGING THE PFF CARE CENTER NETWORK** **LEADERS:** Vincent Cottin, MD, PhD; Kevin R. Flaherty, MD, MS; Jesse Roman, MD **PANEL:** Jerry Eu, MD; Pat Furlong; Dave Sherry; John Morthanos
10:00 a.m.–10:30 a.m.	**BREAK / VISIT EXHIBITS**
10:30 a.m.–10:45 a.m.	**POSTER AWARDEE PRESENTATION IV** Poster awardee — TBD by committee during Poster Presentation on Thursday, November 12

saturday > clinical sessions

CLINICAL CARE: NEW AND EVOLVING TREATMENT STRATEGIES

LEADERS: Ganesh Raghu, MD; Luca Richeldi, MD, PhD

10:45 a.m.–10:50 a.m.	**CLINICAL TOPIC I — SESSION LEADER INTRODUCTION** Luca Richeldi, MD, PhD
10:50 a.m.–11:10 a.m.	**COMBINATION THERAPY: A WAY TO CURE IPF** Paul W. Noble, MD
11:10 a.m.–11:30 a.m.	**APPROVED DRUGS FOR IPF: SHOULD THEY BE STUDIED FOR NON-IPF PULMONARY FIBROSIS?** Kevin K. Brown, MD
11:30 a.m.–11:50 a.m.	**NOVEL TARGETS FOR THE FUTURE: WHAT'S PROMISING?** Andrew M. Tager, MD
11:50 a.m.–12:10 p.m.	**PRECISION MEDICINE FOR IPF: DREAM OR REALITY?** Imre Noth, MD
12:10 p.m.–12:15 p.m.	**DISCUSSION, SESSION CLOSING REMARKS** Ganesh Raghu, MD
12:15 p.m.–1:15 p.m.	**PULMONARY FIBROSIS SURVEY SESSION** You must have pre-registered and have a name badge to enter the session. The session will be held in the Cannon-Hart meeting room on the Mezzanine Level. Lunch will be provided at the meeting.
12:15 p.m.–1:15 p.m.	**LUNCH / NETWORKING / VISIT EXHIBITS / ADVOCACY BREAKOUTS**
1:15 p.m.–1:30 p.m.	**POSTER AWARDEE PRESENTATION V** Poster awardee — TBD by committee during Poster Presentation on Thursday, November 12

saturday > clinical sessions

CLINICAL CARE: COMPREHENSIVE CARE — BEYOND PHARMACOLOGICAL THERAPIES

LEADERS: Anne E. Holland, PhD; Steven D. Nathan, MD, FCCP

1:30 p.m.–1:35 p.m.	**CLINICAL TOPIC II — SESSION LEADER INTRODUCTION** Steven D. Nathan, MD, FCCP
1:35 p.m.–1:50 p.m.	**TOWARDS AN IMPROVED QUALITY OF LIFE:** **STARRING OXYGEN THERAPY AND PULMONARY REHAB** Anne E. Holland, PhD
1:50 p.m.–2:10 p.m.	**LUNG TRANSPLANTATION: NUTS AND BOLTS OR…** **THIS IS NUTS, I AM GOING TO BOLT!** David J. Lederer, MD, MS
2:10 p.m.–2:30 p.m.	**PALLIATIVE CARE AND HOSPICE: LOSING OR RETAKING CONTROL?** Kathleen O. Lindell, PhD, RN
2:30 p.m.–2:40 p.m.	**DISCUSSION**
2:40 p.m.–2:45 p.m.	**SESSION CLOSING REMARKS** Anne E. Holland, PhD
2:45 p.m.–3:15 p.m.	**BREAK / VISIT EXHIBITS**

saturday > clinical sessions

CLINICAL CARE: MULTIDISCIPLINARY DIAGNOSIS

LEADERS: Charlene D. Fell, MD, MSc; Marvin I. Schwarz, MD

3:15 p.m.–3:20 p.m.	**CLINICAL TOPIC III — SESSION LEADER INTRODUCTION** Charlene D. Fell, MD, MSc
3:20 p.m.–3:40 p.m.	**PRESENTATION: HOW TO ORGANIZE MDD IN THE REAL WORLD** Charlene D. Fell, MD, MSc
3:40 p.m.–4:00 p.m.	**CASE PRESENTATION I** Abigail R. Lara, MD
4:00 p.m.–4:20 p.m.	**CASE PRESENTATION II** Brett J. Ley, MD
4:20 p.m.–4:40 p.m.	**CASE PRESENTATION III** Kerri A. Johansson, MD
4:40 p.m.–4:45 p.m.	**DISCUSSION AND SESSION OVERVIEW** Charlene D. Fell, MD, MSc; Marvin I. Schwarz, MD; Thomas V. Colby, MD; David A. Lynch, MD
4:45 p.m.–5:00 p.m.	**PFF SUMMIT CLOSING REMARKS** Gregory P. Cosgrove, MD, FCCP

activity information
accreditation information

PFF
SUMMIT 2015
FROM BENCH
TO BEDSIDE

35

accreditation information

PROVIDERSHIP STATEMENTS

Provided by The France Foundation in collaboration with the Pulmonary Fibrosis Foundation for physician credit.

Co-provided by Postgraduate Institute for Medicine in collaboration with the Pulmonary Fibrosis Foundation for nursing contact hours.

ACCREDITATION STATEMENT (PHYSICIANS)

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of The France Foundation and the Pulmonary Fibrosis Foundation. The France Foundation is accredited by the ACCME to provide continuing medical education for physicians.

LEARNING OBJECTIVES

- Explain the pathophysiology of idiopathic pulmonary fibrosis (IPF) based on the most current data

- Accurately diagnose IPF using a systematic approach

- Effectively implement key diagnostic procedures including HRCT scanning and surgical lung biopsy

- Discuss recent evidence for treatments in the management of IPF

- Recognize genetic components of IPF

- Describe the role of lung transplantation in IPF, and the factors that affect candidacy and timing

- Provide patient lifestyle management tools which improve functional status

- Develop a comprehensive approach to the management of IPF, that includes both pharmacologic and non-pharmacologic therapies

- Provide accurate and appropriate care and counsel for patients and their families

activity information

accreditation information

TARGET AUDIENCE

Physicians, researchers, nurse practitioners, registered nurses, and other health professionals.

CREDIT DESIGNATION

PHYSICIANS

The France Foundation designates this live activity for a maximum of 11.75 *AMA PRA Category 1 Credit(s)™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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HOW TO CLAIM CME/CE CREDITS

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For **ANCC CE (NURSES) CREDIT**, a statement of credit will be issued only upon receipt of a completed online activity evaluation form. See instructions below.

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Once logged in, follow these steps:

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3. Click on the activity title when it appears.
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accreditation information

PFF
SUMMIT
FROM BENCH 2015
TO BEDSIDE

37

FEE

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C Boehringer Ingelheim, Genentech, and ImmuneWorks

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45

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47

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FROM BENCH 2015
TO BEDSIDE

49

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51

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57

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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 2015: From Bench to Bedside.*

Subject matter deemed appropriate for poster presentation at the *PFF Summit 2015* 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 have been reviewed by a panel from the PFF's Scientific Advisory Committee (SAC).

POSTER AWARDS

Poster awards will be granted to the top scoring five abstracts:

- 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

POSTER PRESENTATIONS

The top scoring five abstract presenters will also be asked to give a brief presentation of their research at the beginning of one of the HCP sessions on either Friday, November 13 or Saturday, November 14.

DISCLOSURES

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

MAHA ABDALLA, PHARMD, PHD / ASSISTANT PROFESSOR OF PHARMACEUTICAL SCIENCES, DEPARTMENT OF PHARMACEUTICAL SCIENCES / SOUTH COLLEGE SCHOOL OF PHARMACY / KNOXVILLE, TENNESSEE, UNITED STATES

Role of BMP Signaling in Modulating Myofibroblast Survival in Idiopathic Pulmonary Fibrosis

AUTHORS: Maha Abdalla, PharmD, PhD[3], Azza B. El-Remessy, PhD, RPh, FAHA[1,2], Jacob Dunbar, PhD[3]
1 Clinical and Experimental Therapeutics, College of Pharmacy, University of Georgia, Athens, GA, USA
2 Charlie Norwood VA Medical Center, Augusta, GA, USA
3 Department of Pharmaceutical Sciences, South College School of Pharmacy, Knoxville, TN, USA

GENERAL AUDIENCE SUMMARY

OBJECTIVES: Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive disease with severely poor prognosis. Management options are limited to only two recently approved pharmacological agents, supportive care, and lung transplantation. This highlights the importance of understanding the pathogenesis of this multi-factorial disease, and the need for identifying novel therapeutic strategies. Apoptosis-resistant myofibroblast has emerged as central orchestrator in wound healing and fibrosis. Hypertrophic scarring, hallmark of IPF, is partly due to persistent myofibroblast accumulation and subsequent excess deposition of extracellular matrix proteins. Prior evidence identified impaired signaling of bone morphogenetic proteins (BMPs) family in IPF patients. While BMPs normally modulate myofibroblast activation during embryogenesis and wound healing, their role in IPF remains poorly understood. Thus, we investigated whether restoring BMP signaling modulates myofibroblast survival and matrix stiffening in IPF.

METHODS: Mouse embryonic fibroblasts (NIH 3T3), normal human lung fibroblasts (HLF), and fibrotic HLFs isolated from IPF patients were utilized. Cells were subjected to serum starvation in the presence or absence of TGFß +/- BMP7 for 24, 48, and 72 hrs. The expression of aSMA and its transcription factor SRF, ECM components (Fibronectin EDA and Collagen III), BMP signaling inhibitor (gremlin) and apoptosis-regulating proteins (proNGF/NGF and survivin) were assessed using western blotting and immunofluorescence imaging.

RESULTS: TGFß increased aSMA and ECM protein expression in NIH 3T3, normal and fibrotic HLFs. This was associated with increased gremlin and survivn expressions. BMP-7 treatment decreased aSMA and ECM fibronectin ED-A expressopm level in a dose dependent manner. This was associated with decreased survivin levels. Currently, we are investigating the cross-talk between BMP-7 and pro-NGF/mature-NGF on modulating myofibroblast survival in vitro and in vivo.

CONCLUSION: Our data suggest that impaired BMP signalling may contributue to persistant myofibroblast accumulation and ECM deposition. Thus, restoring BMP signalling could be a potential therapeutic strategy in IPF.

AYODEJI ADEGUNSOYE, MD / POST-DOCTORAL FELLOW, PULMONARY AND CRITICAL CARE /

THE UNIVERSITY OF CHICAGO / CHICAGO, ILLINOIS, UNITED STATES

Altered CD4+ T cell Subpopulations in Lungs of Patients with Idiopathic Pulmonary Fibrosis

AUTHORS: Ayodeji Adegunsoye, MD; Cara L. Hrusch; Catherine Bonham; Mohammed Jaffery; Kelly M. Blaine; Anne I. Sperling

GENERAL AUDIENCE SUMMARY

OBJECTIVES: Idiopathic pulmonary fibrosis (IPF) is a progressive and fatal lung disease of unknown cause. T cell specific gene expression has been found to predict outcomes in IPF patients(1) and CD4+ T cells have been shown to play a central role in murine models. It has been suggested that both Th2 and Th17 cells contribute to IPF pathogenesis, however direct examination of this hypothesis in lungs from patients with IPF has not been tested. Our objective was to determine if CD4+ T cell subsets are altered within the lungs and draining lymph nodes (dLN) in IPF compared to non-IPF controls.

METHODS: We utilized cryopreserved leukocytes isolated from explanted lungs and dLN from ten IPF patients and compared them to non-transplantable, non-diseased donor lungs, matched based on age, gender and smoking status. By performing flow cytometry analysis, using chemokine receptors as a surrogate for CD4+ T cell subsets as previously established(2), we compared these subsets in patients with IPF to controls. Of the CD4+ T cells, Th1 cells were identified as CCR6-CCR4-CXCR3+ cells, Th2 cells as CCR6-CCR4+CXCR3- cells, Th17 as CCR6+CXCR3- cells, non-conventional Th1* cells as CCR6+ CXCR3+ cells and Treg as FoxP3+CD127+ cells. Two unknown subpopulations were also identified.

RESULTS: Analyses revealed a dramatic increase in the percent of CD4+ T cells within IPF lungs compared to control lungs (p = 0.017). Furthermore, the percentage of Th2 cells was significantly elevated in IPF lungs (p = 0.0076). Analysis of the Th17 subset revealed an unexpected reduction in the percent of Th17 cells within both the IPF lungs and their dLN when compared to controls. Strikingly, we found a threefold increase in Tregs within the dLN of patients with IPF compared to controls (p = 0.0005) but this difference was not found in the lungs.

CONCLUSIONS: Our data suggests that Th2 cells, but not Th17 cells, may be predominantly involved in the pathogenesis of IPF in human lungs. Further, the differences found between lungs and dLN suggests that a defect in the trafficking of immune cells may contribute to the process that limits fibrosis to the lungs in IPF.
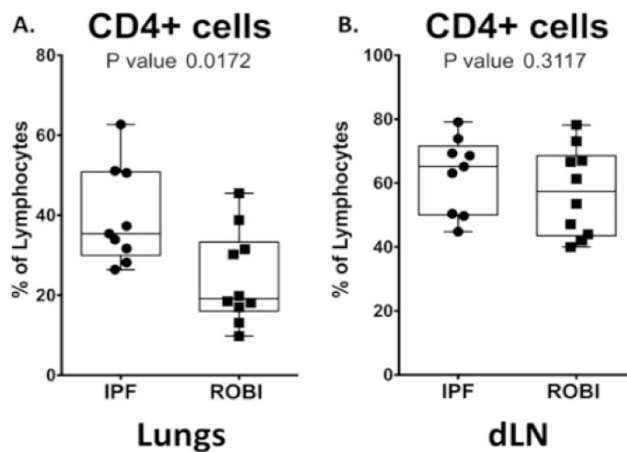
Figure 1. Percentage of CD4+ T cells among total lymphocytes within (A) lungs and (B) draining lymph nodes (dLN) in patients with IPF compared to matched control donor lungs from the Regional Organ Bank of Illinois (ROBI). Data analysis performed by the Wilcoxon–Mann–Whitney test.

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poster presentation abstracts
academic posters

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FROM BENCH 2015
TO BEDSIDE

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JOSE BADDINI-MARTINEZ, MD / HEAD OF CLINIC, PULMONARY DIVISION, INTERNAL MEDICINE / MEDICAL SCHOOL OF RIBEIRAO PRETO – UNIVERSITY OF SAO PAULO / RIBEIRAO PRETO, BRAZIL

Can radiological signs of small airways disease be an initial marker for familial pulmonary fibrosis?

AUTHORS: Jose Baddini-Martinez, MD; Ana B Hortense; Fernanda Gutierrez; Marcel K Santos; Rodrigo T Calado

GENERAL AUDIENCE SUMMARY

OBJECTIVES: Recognition of early features of pulmonary fibrosis has become important, as new drugs are available for treatment. Familial pulmonary fibrosis (FPF) represents a unique opportunity for detecting subjects with asymptomatic disease. This study aimed at characterizing chest CT features in a pedigree with telomere disease, and to correlate these findings with clinical and laboratory features.

METHODS: A 35-years old male diagnosed with aplastic anemia and interstitial pneumonia (IP) died of respiratory failure. Investigation revealed that he had very short telomeres and carried a heterozygous R865H mutation in TERT, previously described as pathogenic (Tsakiri et al., 2007). Family members were screened and high resolution CTs, spirometries, and clinical data were obtained from the additional 21 relatives, covering three generations. Telomere length was measured by flow-FISH methodology and reported according age percentiles.

RESULTS: Radiologic abnormalities were detected in 11 of 22 (50%) family members. The proband had severe IP inconsistent with UIP and his father presented emphysema and possible UIP. These were the only two subjects who had abnormal DLCO (27% and 71%) and rales on physical exam. Suggestive radiologic findings of small airways disease were detected in six subjects with no expressive symptoms and normal pulmonary function tests. Among them, one subject carried the R865H mutation and had very short telomeres. Two of them had short telomeres and the other three exhibited no mutation or telomere shortening. None of the subjects with small airways disease signs reported past or present smoking or other significant environmental exposure. In addition, small-calcified nodules were detected in six among 11 relatives, four of them with short telomeres or TERT mutations.

CONCLUSIONS: Abnormal radiological findings were common in a FPF pedigree associated with the TERT R865H mutation. High-resolution CTs showed higher sensitivity to detect abnormalities than clinical data and pulmonary function tests. Radiological findings of small airways disease were common, and this might be a new sign of very early IP in the telomere dysfunction scenario. Meaning of small calcified nodules is uncertain due to the epidemiology of tuberculosis in Brazil.

MICHAEL FRANCIS BEERS, MD / DIRECTOR OF FELLOWSHIP RESEARCH TRAINING, PULMONARY AND CRITICAL CARE DIVISION, DEPARTMENT OF MEDICINE / THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA / PHILADELPHIA, PENNSYLVANIA, UNITED STATES

Expression Of A Non-Aggregating Surfactant Protein C Mutant Results in Aberrant Alveolar Type 2 Cell Quality Control and Parenchymal Lung Remodeling

AUTHORS: Michael F. Beers; Shin-Ichi Nureki; Yaniv Tomer; Surafel Mulugeta

GENERAL AUDIENCE SUMMARY

OBJECTIVES: Intrinsic lung epithelial cell injury, dysfunction, and/or death are intimately involved in the pathophysiology of diffuse parenchymal lung disease (DPLD) in adults (including idiopathic pulmonary fibrosis (IPF) and children (chILD)). The SFTPC mutation, 218T>C, resulting in a missense substitution of isoleucine to threonine at position 73 [I73T] in the SP-C proprotein [proSP-C]) accounts for approximately 50% of disease-associated SFTPC mutations. Previously we had shown in vitro that SP-C I73T is mistrafficked to late endosomes and produces a block in macroautophagy and mitophagy.

METHODS: To define the cellular consequences of expression of SP-CI73T for the lung in vivo recombineering strategies were employed to selectively knock-in (KI) HA-tagged mouse SP-CI73T into the mouse sftpc locus. While allelic expression (50-100% /WT mRNA) of HA-mSP-CI73T produced dose dependent pulmonary toxicity in utero, hypomorphic expression of SP-CI73T (= 10%/WT) resulted in survival to adulthood. The cellular phenotype and lung structure of SP-CI73THypo mice were assessed at 8, 16, and 32 weeks of age.

RESULTS: Histologically, SP-CI73THypo demonstrated time-dependent appearance of a diffuse cellular infiltration and Trichrome (+) material within alveolar septae. By fluorescence IHC, in contrast to proSP-CWT which was expressed in lamellar bodies of AT2 cells, abnormal trafficking of mutant SP-CI73T proprotein was manifested by its prominent localization in plasma. Subcellular fractionation and Western blotting confirmed that SP-CI73T was misprocessed and excluded from lamellar bodies. By transmission EM, SP-CI73T lungs exhibited hypertrophic AT2 cells with giant autophagosomes containing mitochondria and proteinacious debris which phenocopied AT2 cells from a patient with SP-CI73T related DPLD. In flux assays, SP-CI73THypo AT2 cells demonstrated a functional block in macroautophagy. We conclude that expression of SFTPC I73T in vivo in mice produces AT2 cell ultrastructural abnormalities, aberrant proSP-C trafficking and processing, and dose dependent lung toxicity including disrupted lung morphogenesis and DPLD.

CONCLUSIONS: These results offer proof of concept that AT2 specific gene mutation products create a vulnerable alveolar epithelia which can contribute to the pathogenesis of IPF and chILD.

ELIZABETH BELLOLI, MD / CLINICAL INSTRUCTOR, PULMONARY AND CRITICAL CARE MEDICINE, DEPARTMENT

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Current diagnostic approaches in ILD: ILD versus non-specialty clinics

AUTHORS: Elizabeth Belloli[1]; Michael Rosenbluth[2]; Yoonha Choi[2]; Sherry Danese[3]; Fernando Martinez[1,4];
Kevin Flaherty[1]

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3 Outcomes Insights

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GENERAL AUDIENCE SUMMARY

OBJECTIVES: The approach to diagnosing ILDs has evolved. While high resolution computed tomography (HRCT) and multidisciplinary discussion are key components in the diagnostic process, the approval of pirfenidone and nintedanib for idiopathic pulmonary fibrosis (IPF) has spurred greater urgency to improve the diagnostic process.

METHODS: We conducted a national survey of ILD and non-specialty pulmonologists to assess current ILD diagnostic practices and impact of a novel diagnostic test. Participants were pulmonologists who evaluated at least 10 ILD patients annually. 76 physicians satisfied the screening criteria and completed surveys between March 17-20, 2015 (16 ILD pulmonologists; 60 non-specialty pulmonologists).

RESULTS: ILD physicians diagnosed more patients with ILD (median 100 vs. 43 patients, p=0.017) and IPF (median 40 vs. 20 patients, p=0.02) annually than non-specialty pulmonologists. HRCT was highly utilized in both clinic types (96% vs. 91%, p=0.08). ILD clinicians utilized invasive diagnostic procedures significantly less than non-speciality pulmonologists: bronchoalveolar lavage (BAL), 30% vs. 40% (p=0.022); transbronchial biopsy (TBB), 27% vs. 41% (p=0.002); surgical lung biopsy (SLB), 32% vs. 42% (p=0.021).

Clinicians were provided clinical backgrounds and HRCT images for 4 patient cases and were queried regarding diagnostic/treatment plans. ILD pulmonologists were more likely to recommend pirfenidone or nintedanib for patients with definite usual interstitial pneumonia (UIP) on HRCT than non-specialty pulmonologists (81% vs. 38%, p=0.006). 48% of non-specialty pulmonologists recommended BAL/ TBB or SLB in this patient case despite classic clinical history and typical IPF HRCT findings. In cases of possible UIP, the recommendation to biopsy was high and comparable between groups (53% for ILD pulmonologists vs. 61% for non-specialty pulmonologists, p=0.558). Table 1 illustrates the diagnostic or therapeutic approaches for various clinical scenario and HRCT combinations for clinicians in both care settings.

CONCLUSIONS: Diagnostic and therapeutic approaches utilized by ILD and non-specialty pulmonologists in ILD evaluation differ. Enhanced strategies to evaluate ILDs are required as the field rapidly evolves.

Diagnostic or therapeutic approach	ILD pulmonologists	Non-specialty pulmonologists
HRCT/Clinical scenario – Possible UIP/IPF		
BAL/TBB	6.3%	31.7%
SLB	43.8%	30.0%
Treat with pirfenidone or nintedanib	18.8%	8.3%
Treat with immunosuppressive medications	6.3%	1.7%
Monitor without further intervention	18.8%	23.3%
Other	6.3%	5.0%
HRCT/Clinical scenario – Definite UIP/IPF		
BAL/TBB	18.8%	26.7%
SLB	0%	21.7%
Treat with pirfenidone or nintedanib	81.3%	38.3%
Treat with immunosuppressive medications	0%	5.0%
Monitor without further intervention	0%	5.0%
Other	0%	3.3%
HRCT/Clinical scenario – Possible UIP versus Hypersensitivity pneumonitis		
BAL/TBB	6.3%	30.0%
SLB	50.0%	30.0%
Treat with pirfenidone or nintedanib	18.8%	31.7%
Treat with immunosuppressive medications	12.5%	0%
Monitor without further intervention	6.3%	5.0%
Other	6.3%	3.3%
HRCT/Clinical scenario – Possible UIP/Clear connective tissue associated-ILD		
BAL/TBB	18.8%	20.0%
SLB	12.5%	28.3%
Treat with pirfenidone or nintedanib	12.5%	10.0%
Treat with immunosuppressive medications	37.5%	33.3%
Monitor without further intervention	0%	5.0%
Other	18.8%	3.3%

Table 1: Diagnostic or therapeutic approaches of ILD pulmonologists and non-specialty pulmonologists in the evaluation of ILDs.
Definitions of abbreviations: BAL: Bronchoalveolar lavage; SLB: Surgical lung biopsy; TBB: Transbronchial biopsy.

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Inducible T-cell costimulator (ICOS) expression on CD4 T cells predicts outcomes in idiopathic pulmonary fibrosis

AUTHORS: Catherine Bonham, MD; Cara Hrusch, PhD; Stephenie Takahashi, MD; Kelly M. Blaine, MS; Matthew M. Churpek MD, PhD; Imre Noth, MD; Mary Strek, MD; Anne I. Sperling, PhD

GENERAL AUDIENCE SUMMARY

OBJECTIVES: Predicting idiopathic pulmonary fibrosis (IPF) progression through blood biomarkers may provide improved understanding of disease mechanisms and allow directed interventions for the patients most likely to progress. Previous gene expression studies have suggested a role for the inducible costimulatory molecule (ICOS) in IPF survival. Our objective was to determine if surface expression of ICOS predicts disease progression and survival.

METHODS: Blood mononuclear cells from 60 IPF patients and 22 age-matched controls were analyzed by flow cytometry for surface expression of CD4, CD45RO, CD28, and ICOS. Repeated measures of these markers and pulmonary function tests (PFTs) were analyzed using mixed effect regression models controlling for the fixed effects of age, sex, race, smoking history, and steroid use over time. Survival analysis was performed with unadjusted log rank test and plotted using the Kaplan-Meier survival estimator. Survival time was defined as the time from first blood draw until death, and patients were censored at time of transplant or study end.

RESULTS: While there was no difference in co-stimulatory receptors on IPF versus control CD4+ T cells, within the IPF cohort ICOS surface expression correlated with declining FVC ($p=0.029$) and DLCO ($p=0.001$) (Figure 1). ICOS expression on CD4+ T cells decreased in association with declining PFTs in both mature CD45RO+ and immature CD45RO- T cells, suggesting that the effect of ICOS was independent of upstream shifts in memory T cell activation. ICOS expression on CD4+ T cells decreased significantly on CD28+ cells, but not CD28- cells, demonstrating that ICOS down regulation in progressive IPF patients is not driven by an increase in previously reported CD4+CD28- or "null" cell populations. Surprisingly, the 20% of IPF patients with the highest levels of ICOS expression on CD4+ T cells at study entry had markedly improved survival outcomes ($p=0.02$) (Figure 2).

CONCLUSION: ICOS expression on peripherally circulating CD4 T cells is both significantly associated with PFT decline and predicts survival of IPF patients. These findings suggest that patients with low to intermediate ICOS expression on CD4 T cells should be targeted for novel therapeutic trials.

Figure 1: Decreased surface expression of ICOS on CD4+ lymphocytes is significantly associated with decline in pulmonary function. Mixed effect regression models controlling for age, sex, race, steroid use, and smoking history reveal that decreased ICOS expression independently associates with IPF disease progression as measured by decline in A. forced vital capacity (FVC) and B. diffusing capacity of the lung for carbon monoxide (DLCO) over time.
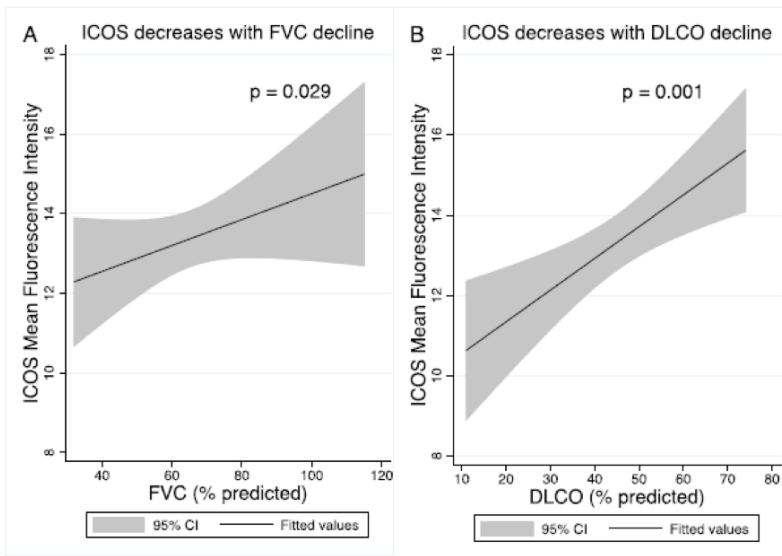
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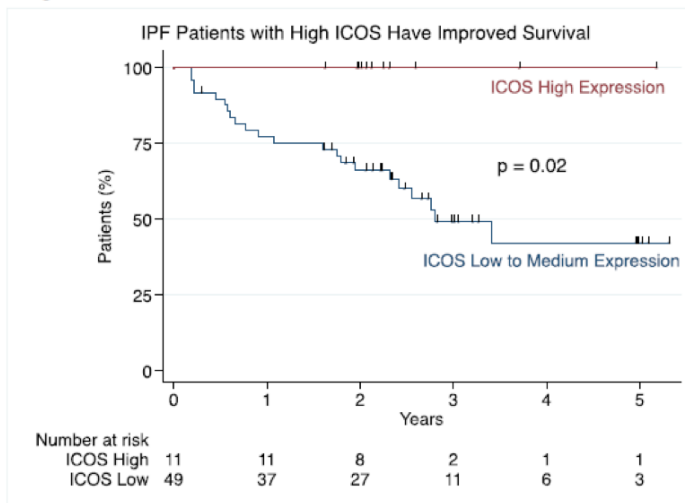
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Curcumin, aspirin, and sulforaphane combined mechanism of apoptosis in idiopathic pulmonary fibrosis (IPF) fibroblasts

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GENERAL AUDIENCE SUMMARY

OBJECTIVES: Curcumin has been shown to have anti-fibrotic properties; however its bioavailability limits its application as a therapeutic for IPF. We sought to enhance curcumin's (CUR) apoptotic capabilities and reveal its mechanism via combination with aspirin (ASA) and sulforaphane (SFN) (CAS) in IPF and normal primary human fibroblasts in vitro.

METHODS: Normal (N-F, n=3) and IPF (IPF-F, n=3) fibroblast cells were exposed for 48 hrs to CAS (3mM ASA, 20µM CUR, 40µM SFN), a combination of drugs that individually were nonlethal. Fibroblast cell survival was determined by Cell Titre Glo™ assay. Markers for cell survival and apoptosis were analyzed by Western blot and Q-PCR.

RESULTS: Exposure of cells to CAS resulted in a 73.97±31.31% (p=0.0474*) and 49.64 ±6.87% (p=0.0021*) decrease in N-F and IPF-F cell survival respectively. Exposure to CAS in N-F resulted in an overall down-regulation in activation of the NFkß pathway, a 2.0-1.5 fold reduction of phosphorylated AKT and a 2 fold increase in GSK-3 phosphorylation. Conversely IPF-F cells demonstrated an increase in NFkß pathway activation post exposure in addition to a 1.5 fold increase in AKT phosphorylation. GSK-3 activity was unchanged. CAS exposure also resulted in a 5.5 and 1.5 fold activation of the MAPK cascade: extracellular signal regulated kinase (ERK) 1/2 in N-F and IPF-F respectively. A 6 fold increase in caspase 7 cleavage was observed in IPF-F while N-F demonstrated a 1.3 fold activation of caspase 7.

CONCLUSIONS: CAS combined exposure over 48 hours resulted in a significant increase in cell death in both N-F and IPF-F. The differential activation of ERK1/2 pathway may play a role in the degree of cell death demonstrated. However IPF-F appear to be more resistant to CAS induced apoptosis when compared to N-F. The difference in cell survival may be attributed to increase activation of the NFkß pro-survival pathway via potential crosstalk between PI3K-AKT and NFkß pathways. The contrasting routes of apoptosis observed, highlight a significance difference between these cell types. Further understanding of the apoptotic mechanisms in IPF will identify cell specific targets for the directed elimination of IPF-F while preserving the integrity of the N-F population.

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Vaccinia immunotherapy reverses bleomycin induced pulmonary fibrosis and improves lung function

AUTHORS: Collins S; Chan-Li Y; Vigeland C; Horton MR

GENERAL AUDIENCE SUMMARY

RATIONALE: Pulmonary fibrosis is a progressive, fatal disease that primarily affects elderly patients and is due to dysregulated chronic inflammation of the lungs. Current therapies focus on slowing the ongoing accumulation of lung collagen, rather than halting or ideally, reversing existing lung fibrosis. One reason for the absence of effective therapies is a lack of understanding of the pathophysiology leading to fibrosis. What has become clear is the importance of the immune system in both the development and resolution of this disease. There are numerous observations in animal models and in patients that describe an association of pulmonary fibrosis with T lymphocyte infiltration. However, the nature of the inflammatory milieu appears to determine whether T cells will promote or diminish the pulmonary fibrotic process. We have previously demonstrated that promotion of a Th1 environment in the lung by utilizing immunotherapy with intranasal vaccinia virus abrogates the development of pulmonary fibrosis in an intratracheal model of bleomycin induced pulmonary fibrosis. In light of these data, we sought to evaluate the therapeutic effect of immunomodulation on progressive and established lung fibrosis.

METHODS: We utilized a mouse model of intraperitoneal (IP) injections of bleomycin over the course of four weeks that leads to subsequent progressive lung fibrosis at 42 -72 days. This model differs from an intratracheal bleomycin model as it avoids the initial acute inflammation by causing sub-acute inflammation resulting in lung fibrosis. We analyzed the ability of vaccinia immunotherapy to improve pulmonary fibrosis by analyzing lung collagen concentrations as well as pulmonary function testing.

RESULTS: Vaccinia immunotherapy reversed IP bleomycin induced collagen deposition in the lung. In addition, vaccinia immunotherapy significantly improved lung function as measured by diffused capacity, lung resistance, and lung compliance.

CONCLUSIONS: Our data point to T cell skewing as an important immunotherapy target.

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71

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Pirfenidone post-authorization safety registry (PASSPORT) update

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GENERAL AUDIENCE SUMMARY

OBJECTIVES: PASSPORT is a post-authorization safety registry for pirfenidone to collect "real-world" data in EU patients with idiopathic pulmonary fibrosis (IPF). The objectives of this study were to: 1) assess the safety of pirfenidone as monotherapy and with N-acetylcysteine (NAC) and/or corticosteroids and 2) examine country-specific differences.

METHODS: 109 European Union sites dosed 1006 patients; the largest enrolling countries were Germany (N=451), France (N=214) and the United Kingdom (N=183). Safety data were recorded at routine clinic visits for up to 2 years. Adverse drug reactions (ADR; noxious, unintended drug response) were collected.

RESULTS: At baseline, mean±SD age was 70±8.5 years and time since IPF diagnosis 1.6±2.5 years; 80% were male; supplemental oxygen was used by 27%; mean±SD forced vital capacity (FVC) was 2.56±0.78 L; mean±SD % predicted FVC was 66±16% (14% of patients had %FVC<50%). The most common comorbidities (>10%) were hypertension, gastroesophageal reflux disease, hypercholesterolemia and coronary artery disease.

At this interim analysis, median time patients received pirfenidone was 7.6 months; total exposure was 803 patient-years. 62% of patients received pirfenidone alone; 11%, 8% and 8% also received NAC, oral corticosteroids and NAC+corticosteroids, respectively. ADR incidence was generally consistent for these subgroups except weight decrease which occurred more often in the pirfenidone+corticosteroids group (19.5% vs 8.1%-11.8%). Two-thirds had >=1 ADR; the most common were nausea, 17%; fatigue, 15%; decreased appetite, 13%; decreased weight, 12%; rash, 10%; and diarrhea, 9%.

Patient characteristics and ADRs were similar in the 3 largest enrolling countries (Germany, France and the United Kingdom).

CONCLUSION: In this real-world setting, pirfenidone was generally safe and well tolerated as monotherapy or combined with NAC and/or corticosteroids. Characteristics and safety profile of German, French and United Kingdom patients were similar.

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Idiopathic Pulmonary Fibrosis: Using Electronic Health Records for Clinical Research in Rare Diseases

PRESENTER: Shaquille Charles

AUTHORS: Sonye K. Danoff, MD, PhD; Harold Lehmann, MD, PhD

GENERAL AUDIENCE SUMMARY

Electronic Health Records (EHRs) were used to identify patients with idiopathic pulmonary fibrosis (IPF), a rare lung disease that affects only .028% of Americans in the United States. An IPF Computable Phenotype Algorithm was developed based on ICD-9 codes to identify IPF patients from EHRs at a single large tertiary care institution. The algorithm's efficiency was evaluated by reviewing its sensitivity and specificity among identified IPF patients by practicing physicians specializing in Interstitial Lung Diseases (ILD). A list of patients with known IPF was cross-referenced with a list of IPF patients derived from the IPF Computable Phenotype Algorithm. Specificity was evaluated by computing the algorithm's positive predictive value (PPV), sensitivity was assessed by computing the algorithm's true positive rate (TPR), and in order to confirm that the algorithm's lens was narrow enough, we also computed the false positive rate (FPR). We hypothesized that by utilizing characteristics of the rare disease as well as evaluating the algorithm's trend of false positives and false negatives, we will be able to develop an algorithm that can accurately identify eligible IPF patients from EHRs.

METHODS: Electronic Health Records are exported from EPIC into the Informatics for Integrating Biology and the Bedside (i2b2) database. The algorithm then identifies patients with IPF. Physicians evaluate how well the algorithm captured patients from an existing IPF registry and whether all identified patients truly have IPF. Patient EHRs that were incorrectly identified as well as IPF patients that should have been identified were reviewed and the algorithm modified. Positive predictive value (PPV), true positive rate (TPR), and false positive rate (FPR) were then reassessed.

RESULTS: By adding both inclusion and exclusion criteria, accuracy significantly increased from a PPV of 63.6% to a PPV of 88.2%. TPR increased from 49.3% to 63.4%.

CONCLUSION: In order to assess a Computable Phenotype's accuracy, the results must be validated with an existing registry. Utilizing EHRs to conduct clinical research allows for an unbiased method of patient recruitment. Future research should validate this Computable Phenotype by applying it to EHRs from different institutions.

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Clinical Characteristics and Disease Burden of Newly Diagnosed IPF at Tertiary Care Centers: Initial Results from the Idiopathic Pulmonary Fibrosis—PROspective Outcomes (IPF-PRO) Registry

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GENERAL AUDIENCE SUMMARY

OBJECTIVES: Idiopathic pulmonary fibrosis (IPF) is often diagnosed after multidisciplinary evaluation at tertiary care centers. Little is known about the characteristics of patients with IPF at the time of diagnosis in the United States. We examined the clinical course leading to a diagnosis of IPF, including diagnostic evaluations, physiologic measures, symptoms and quality of life, among patients enrolled in the national, multi-center IPF-PRO registry.

METHODS: We analyzed data from the first 49 patients enrolled in the IPF-PRO registry from 10 US centers between June 2014 and March 2015. All patients were newly diagnosed with IPF, or had their outside diagnosis confirmed, at the enrolling center. Diagnostic evaluations in the 12 months preceding enrollment, and demographic and physiologic measures at the time of diagnosis were abstracted from medical records. Patients completed the St. George's Respiratory Questionnaire (SGRQ) and the cough domains of the Cough and Sputum Assessment Questionnaire (CASA-Q). We report descriptive statistics as n (%) for categorical variables and median (IQR) for continuous variables.

RESULTS: Baseline characteristics are shown in Table 1. Patients were predominantly male, with a median age of 72 (67-75) years. Median time from onset of respiratory symptoms to IPF diagnosis at the subspecialty clinic was approximately 16 months. Nearly all subjects (98%) had undergone high-resolution chest CT (HRCT), while 20% had undergone surgical biopsy. Median FVC was 72% (61-81%) predicted and DLCO (corrected for hemoglobin) was 39% (34-48%) predicted. The most commonly reported comorbidities were gastroesophageal reflux disease (69%), coronary artery disease (31%), and sleep apnea (29%).

Among the 45 patients with complete data, the median SGRQ score was 40.7. CASA-Q scores demonstrated substantial cough symptom burden (median score 58.3) and impact on well-being (median score 75.0) (Table 2).

CONCLUSIONS: The majority of new IPF diagnoses made at tertiary care centers were based on HRCT and clinical information. Most patients had respiratory symptoms for greater than one year prior to diagnosis, and substantial physiologic impairment, comorbidity, quality of life impact, and cough burden at the time of tertiary center diagnosis.

TABLE 1: Baseline demographic and disease characteristics.

Baseline Demographics and Disease Characteristics	n (%) Median (IQR) (n=49)
Gender	
• Male	36 (73%)
• Female	13 (27%)
Age (years)	72 (67-75)
History of smoking	39 (80%)
Time from first respiratory symptoms to IPF diagnosis at enrolling center (months)	16.4 (9.8-19.0)
Components of diagnostic evaluation	
• High-resolution chest CT	48 (98%)
• Surgical lung biopsy	10 (20%)
Pulmonary function	
• FVC (% predicted)	72 (61-81)
• DLCO (% predicted)	39 (34-48)
Six-minute walk distance (m)	358 (291-454)
Supplemental oxygen needed	
• At rest	14 (29%)
• With activity	22 (45%)
Comorbidities	
• Gastroesophageal reflux disease	34 (69%)
• Coronary artery disease	15 (31%)
• Sleep apnea	14 (29%)
• COPD	9 (18%)

TABLE 2: Patient-reported outcomes.

Patient-reported outcome	Median (IQR) (n=45)
St. George's Respiratory Questionnaire total score	40.7 (26.3-52.3)
Cough and Sputum Assessment (CASA-Q) Questionnaire score	
• Cough symptoms	58.3 (50.0-75.0)
• Cough impact	75.0 (56.3-90.6)

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75

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The effect of pirfenidone on AKR-2B fibroblast extracellular matrix production and TGFß signaling pathways

AUTHORS: Megan Girtman, MD; Theodore J. Kottom, PhD; Deanne M. Hebrink; Paige E. Jenson;
Andrew H. Limper, MD

GENERAL AUDIENCE SUMMARY

BACKGROUND: Idiopathic pulmonary fibrosis (IFP) is a progressive fibroproliferative lung disease with no known cure. Recent studies in IPF patients treated with pirfenidone have shown a delay in disease progression. Experiments done in fibroblasts in vivo have demonstrated pirfenidone treatment decreases extracellular matrix production indicating a potential role for the TGF-ß signaling pathway.

OBJECTIVE: We hypothesize that pirfendione treatment alters protein expression downstream from the TGF-ß receptor resulting in decreased extracellular matrix production.

METHODS: Experiments were done in AKR-2B mouse fibroblasts or MRC-5 human fibroblasts. Cells were incubated with pirfenidone for 60 minutes and then treated with TGF-ß1. Cells were harvested after 6 hours for measurement of protein level, mRNA and miRNA expression or ELISA. For colony formation assays, cells were grown in soft agar containing media and total colonies were counted after 8 days.

RESULTS: AKR-2B cells treated with pirfenidone have decreased extracellular matrix production detected by Western blot, ELISA, and qPCR. Cells also form fewer colonies than non-treated cells in a soft agar colony formation assay. Probing protein levels downstream of the TGF-ß receptor reveled altered expression in both SMAD dependent and SMAD-independent pathways. Pirfenidone treated cells have decreased pSMAD3 levels in the nucleus. Analysis of SMAD independent pathways revealed decreased pp70S6k protein levels. PP2A is known to dephosphorylate p70S6k and as expected, levels of PP2A are increased in cells treated with pirfenidone. A second target of PP2A is HDAC4. Dephosphorylation of HDAC4 leads to nuclear accumulation. Protein levels of HDAC4 are increased in cells treated with the drug. HDAC4 targets miR-29, a known regulator of collagen expression. Cells treated with pirfenidone have increased levels of HDAC4.

CONCLUSIONS: Pirfenidone decreases the production of extracellular matrix proteins in AKR-2B fibroblasts. This decrease may be attributed to the effect pirfenidone has on both SMAD-dependent and independent pathways downstream of the TGF-ß receptor. SMAD dependent analysis revealed decreased levels of pSMAD3 in the nucleus. SMAD-independent signaling proteins were alt

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Pirfenidone is efficacious in patients with idiopathic pulmonary fibrosis (IPF) with more preserved lung function

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GENERAL AUDIENCE SUMMARY

OBJECTIVES: IPF is a progressive, irreversible and fatal disease. Early treatment initiation when lung function is relatively preserved may have beneficial outcomes; however, published data to support this hypothesis are lacking. We investigated the efficacy of pirfenidone at 12 months in patients stratified by lung function using forced vital capacity (FVC) or GAP stage.

METHODS: Efficacy outcomes (FVC, 6-minute walk distance [6MWD] and dyspnea [UCSD SOBQ]) were analyzed at 12 months in patients randomized to pirfenidone 2403 mg/d or placebo in the pooled CAPACITY/ASCEND population (N=1247), stratified by baseline FVC (>=80%, <80%) and GAP stage (GAP I, GAP II-III). Treatment-by-subgroup interaction was tested based on a rank ANCOVA model. The factors in the model included study, region, treatment, subgroup and treatment-by-subgroup interaction term.

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.... 77

RESULTS: Demographic characteristics were similar across all four groups. In the placebo arm, disease progression as measured by FVC occurred with comparable frequency in patients with FVC >=80% and FVC <80%, as well as in patients with GAP I and GAP II-III stage. A higher proportion of placebo patients with FVC <80% and GAP II-III stage had a >=50-m decline in 6MWD or death or a >=20-point change in the UCSD SOBQ total score. Pirfenidone treatment reduced the proportion of patients experiencing a >=10% FVC decline or death and increased the proportion of patients with no FVC decline in all subgroups. Pirfenidone also reduced the proportion of patients with >=50-m decline in the 6MWD or death and increased the proportion of patients with no 6MWD decline in all subgroups. The magnitude of treatment effect in patients with less vs more preserved lung function was comparable, with no significant treatment-by subgroup interaction (Figure).

CONCLUSIONS: In the placebo population, clinically significant disease progression occurs in subgroups with more and less preserved lung function at baseline, underlying the need for early intervention. The magnitude of pirfenidone treatment effect on functional measures was comparable in both subgroups of patients (FVC <80% vs FVC >=80% or GAP I vs GAP II-III stage), supporting treatment initiation soon after diagnosis, when pulmonary function is relatively preserved.

Figure. Treatment effect of pirfenidone by baseline lung function

Outcome	Subgroup	Standardized Treatment Effect*	Treatment Effect P Value[†]	Interaction P Value[‡]
FVC	FVC < 80%		< 0.0001	0.3969
	FVC ≥ 80%		< 0.0001	
	GAP stage II-III		< 0.0001	0.8152
	GAP stage I		< 0.0001	
6MWD	FVC < 80%		0.0011	0.9583
	FVC ≥ 80%		0.0514	
	GAP stage II-III		0.0074	0.9327
	GAP stage I		0.0197	
UCSD SOBQ	FVC < 80%		0.0053	0.1957
	FVC ≥ 80%		0.8929	
	GAP stage II-III		0.0096	0.0804
	GAP stage I		0.9767	

−1.0 −0.5 0.0 0.5 1.0
← Favors Placebo   Favors Pirfenidone →

6MWD, 6-minute walk distance; FVC, forced vital capacity; UCSD SOBQ, University of California—San Diego Shortness of Breath Questionnaire.
*For FVC and 6MWD: treatment difference = pirfenidone − placebo; for UCSD SOBQ, treatment difference = placebo − pirfenidone.
[†]P values represent categorical difference (pirfenidone *versus* placebo). Percentage relative treatment difference in the proportion of patients achieving efficacy outcomes were calculated using the following formula: 100 × [pirfenidone − placebo]/[placebo].
[‡]The P value is from the test statistic for testing the interaction between the treatment and subgroup variable.

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Fibroblast-specific FGF signaling in bleomycin-induced pulmonary fibrosis

AUTHORS: Robert Guzy; David M. Ornitz

RESEARCH SUPPORT: American Heart Association Fellow-to-Faculty Transition Award; ATS Foundation Recognition Award

GENERAL AUDIENCE SUMMARY

OBJECTIVES: Idiopathic pulmonary fibrosis (IPF) is characterized by progressive pulmonary scarring, and often results in death within three to five years after diagnosis. Recently approved treatments for IPF target Fibroblast Growth Factor (FGF) signaling, however the mechanism through which FGFs contribute to IPF remains unclear. In vitro, FGF signaling interacts with TGF-beta in fibroblasts, but this has not been shown in vivo. We hypothesized that FGF signaling in lung fibroblasts is required for bleomycin-induced pulmonary fibrosis in mice.

METHODS: Mice with tamoxifen-inducible Cre recombinase driven by the promoter for procollagen Ia2 (Col1a2-CreER) were crossed with the ROSA26-mTmG reporter and floxed alleles for FGF receptors 1, 2, and 3 to generate fibroblast-specific Fgfr1/2/3 conditional knockouts. Mice were treated with tamoxifen at P21 to induce gene recombination. At 8–9 weeks of age, mice were exposed to intratracheal bleomycin (1.2 U/kg), and lungs were subsequently inflation-fixed at 20cm H_2O and processed for frozen or paraffin sections. In parallel experiments, lungs were used for flow cytometry or whole-lung RNA or protein was analyzed via qRT-PCR or Western Blot.

RESULTS: Col1a2-CreER targets Periostin+ and aSMA+ peribronchial smooth muscle and fibroblasts, and PDGFRa+ interstitial fibroblasts. The lineage of cells targeted by Col1a2-CreER expands after bleomycin, concentrated in areas of fibrosis. Fibroblast-specific Fgfr1/2/3 conditional knockout mice have efficient deletion of FGFRs 1-3 in response to tamoxifen. After treatment with bleomycin, Fibroblast-specific Fgfr1/2/3 conditional knockout mice have decreased fibrosis and decreased collagen production.

CONCLUSIONS: Col1a2-CreER targets cells in the lung which give rise to fibrotic tissue in response to bleomycin. Our data suggests that intact FGFR signaling in fibroblasts appears to be required for collagen expression and development of fibrosis in response to bleomycin, implicating fibroblast-specific FGF signaling in the pathogenesis of pulmonary fibrosis.

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79

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Inhaled Interferon-gamma Attenuates Pulmonary Fibrosis, Role of Matrix metalloproteinase

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GENERAL AUDIENCE SUMMARY

BACKGROUND: Patients with idiopathic pulmonary fibrosis (IPF) are deficient in interferon-gamma (IFN-gamma) secreted from alveolar epithelial type II cells and lymphocytes. In a two year clinical trial in patients with IPF, we demonstrated that inhaled IFN-gamma is safe and may be effective treatment for IPF patients (Diaz et al J Aerosol Med 2012,(25):,1-9 and Skaria et al. Sarcoidosis Vasc Diffuse Lung Dis 2015; (32): 37-42).

OBJECTIVE: To study the local anti-fibrotic effects of inhaled IFN-gamma by examining bronchoalveolar lavage fluid (BALF) for gene and protein expression before and after treatment with inhaled IFN-gamma in IPF patients.

METHODS: Seven patients with IPF received inhaled IFN- gamma three times a week for 80 weeks. BAL was performed before and during therapy. Gene expression was measured on RNA samples from BALF cellular component using Affymetrix human U133Av2 chips. Protein expression was also studied using zymography, western blot and Luminex assay. BAL soluble collagen content was measured using Sircol assay.

RESULTS: Microarray gene expression demonstrated that IFN-gamma treatment down regulates multiple signal pathways involved in T cell and B cell immunity, actin cytoskeleton, VEGF signaling pathway, apoptosis, PI3 signaling and chemokine C-X-C motif ligands. BAL fluid zymography and western blot show that IFN-gamma inhibited MMP-9, MMP-1 and Osteopontin. IFN-gamma treatment resulted in a marked decrease in BAL fluid collagen content.

CONCLUSION: In humans with IPF, inhaled INF-gamma has potent anti-fibrotic effects via multiple signaling pathways, immune modulatory effects and MMP inhibition. Inhaled IFN- gamma has potential as a novel therapy for IPF.

LOUISE HECKER, PHD / ASSISTANT PROFESSOR, MEDICINE / THE UNIVERSITY OF ARIZONA /

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Impaired Myofibroblast Dedifferentiation Contributes to Non-Resolving Fibrosis in Aging

AUTHORS: Louise Hecker, PhD; Victor J. Thannickal; Naomi Logsdon; Joe. G. N. Garcia

GENERAL AUDIENCE SUMMARY

OBJECTIVES: Idiopathic pulmonary fibrosis (IPF) is a fatal disease, characterized by progressive scar tissue formation leading to respiratory failure. The incidence and prevalence of IPF increase with age. However, the mechanism(s) for this age-associated predilection are not known. Previously, we demonstrated that myofibroblasts retain the capacity for dedifferentiation, which is mediated by downregulation of MyoD. We examined the effect of aging on myofibroblast dedifferentiation and the capacity for fibrosis resolution.

METHODS: We utilized a cellular model of replicative senescence: human lung fibroblasts at low and high population doublings. Cells were treated with TGF-ß1 to induce myofibroblast differentiation, followed by treatment with high or low serum to evaluate the capacity for dedifferentiation. Cellular phenotypes were evaluated by biochemical assays. Young (2m) and aged (18m) mice were subjected to bleomycin-induced lung fibrosis. Intranasal administration of MyoD siRNA in aged mice with persistent fibrosis was utilized to evaluate the role of MyoD in age-associated persistent fibrosis in-vivo. Severity and resolution of fibrosis was assessed at 3 weeks and 2 months post-injury by whole tissue morphology, immunohistochemistry, and biochemical assays. IPF lung tissue and fibroblasts were evaluated for expression of MyoD.

RESULTS: We provide the first evidence, to our knowledge, of an impaired capacity for myofibroblast dedifferentiation in aging. Senescent fibroblasts exhibited an impaired capacity for dedifferentiation associated with apoptosis-resistance, as compared to young. MyoD expression is elevated in aged mice with persistent fibrosis and in IPF patient lung tissue and myofibroblasts. Treatment with MyoD-targeting siRNA in aged mice with established lung fibrosis led to a reversal of age-associated persistent fibrosis.

CONCLUSIONS: The inability to terminate myofibroblast activation/accumulation may underlie the progressive nature of human fibrotic reactions in injured tissues. Our studies indicate that myofibroblast dedifferentiation promotes fibrosis resolution in young mice, whereas sustained upregulation of MyoD in aging leads to impaired myofibroblast dedifferentiation, which confers an apoptosis-resistant phenotype to the

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Accuracy of Community Diagnosis of Idiopathic Interstitial Pneumonias referred to an Academic Medical Center. A Single Center Experience

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GENERAL AUDIENCE SUMMARY

OBJECTIVES: Idiopathic Interstitial Pneumonias (IIPs) are a subgroup of the diffuse parenchymal lung diseases of unknown etiology and are characterized by varying degrees of inflammation and fibrosis. The IIPs have significant heterogeneity in their clinical course based on their specific clinicopathological subtype. A multidisciplinary diagnostic approach and referral to centers of expertise is endorsed by current multi-society guidelines.(1, 2) We sought to determine the diagnostic agreement between community diagnosis and final diagnosis of patients referred to our Interstitial Lung Disease Clinic.

METHODS: We performed a retrospective chart review (September 1, 2014–February 28, 2015) of all new patient visits for two of our physicians (J.H. and T.W.) at the Medical University of South Carolina (MUSC) Interstitial Lung Disease Clinic. We excluded all cases that were not referred by community pulmonologists or referred for non-IIP diagnosis. We reviewed the referral diagnosis and final diagnosis in addition to the clinical, imaging and anatomic pathology data. The initial diagnosis was obtained from the referral notes of the community provider. The final diagnosis was obtained from the ILD clinic note incorporating Thoracic radiology and pathology input.

RESULTS: Of 83 cases reviewed 45 met our inclusion criteria. We excluded 38 cases, 25 that were not referred for an IIP diagnosis, 8 were not referred by a community pulmonologist and 3 we found to be follow-up patients. Mean age 70±12, 62% (28/45) male, 69% (31/45) prior or current smokers, mean FVC % 66 ± 21, mean DLCO % 54 ± 23. We had a 62% (28/45) diagnostic agreement with the community providers. Idiopathic pulmonary fibrosis was the referral diagnosis for the majority of cases 62% (28/45) and diagnostic agreement was higher in this subset 82% (23/28).

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82 ....

CONCLUSIONS: We identified that on evaluation at our ILD center approximately 40% of patients received a alternative diagnosis. Prior studies describe higher diagnostic agreement within physicians at academic centers and an association of higher mortality with delayed access to a tertiary care center.(3, 4) Further research is needed to identify objective methods for improving the diagnostic accuracy of IIP.

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83

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Developing a patient-centered instrument for treatment preferences in idiopathic pulmonary fibrosis

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GENERAL AUDIENCE SUMMARY

OBJECTIVES: To describe the development of a stated preferences survey to measure patient's treatments preferences for idiopathic pulmonary fibrosis (IPF)

METHODS: Patients with IPF were shown draft survey instruments that included best-worst scaling and discrete-choice survey formats. We conducted cognitive-interview with those patients utilizing a checklist and prospective and retrospective probing questions. A pilot survey was developed using qualitative data drawn from the completed surveys, cognitive interview field notes and digital recordings of the interviews. A paper-based pilot survey was sent out to IPF patients from the Johns Hopkins University Interstitial Lung Disease clinic.

RESULTS: Fifteen cognitive interviews of approximately 30 minutes were completed. We found general acceptability of attributes, levels and the survey overall with some preference for best-worst scaling format because it contains less information to evaluate than the discrete-choice format. Respondents also favored reducing the number of attributes. The pilot survey that was developed included an 18-question best-worst scaling experiment of 6 attributes and 3 levels. Seventeen respondents provided pilot data that demonstrated floor and ceiling effects between some of the moderate and significant levels.

CONCLUSIONS: Good research practices for developing stated-preference instruments are under-developed. We use cognitive interviews and pilot study data as a systematic way to engage patients in stated-preference instrument development and incorporate patient perspectives in regulatory benefit-risk assessment.

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Type-2 immune responses protect against bleomycin-induced lung injury through an ICOS-dependent mechanism

AUTHORS: Cara Hrusch; Dana Bryazka; Mohammad R. Jaffery; Catherine A. Bonham; Kelly M. Blaine; Joshua Casaos; Stephenie M. Takahashi-Manns; Anne I. Sperling

GENERAL AUDIENCE SUMMARY

OBJECTIVES: Idiopathic pulmonary fibrosis (IPF) is a progressive lung disease causing irreversible lung scarring and loss of pulmonary function. These patients suffer from a high rate of pulmonary infections and acute exacerbations of disease that further contribute to pulmonary decline. Patients with IPF have reduced ICOS expression in peripheral blood mononuclear cells, but the role of ICOS in pathogenesis is unclear. In this study we examined how ICOS-expressing cells contribute to pulmonary fibrosis.

METHODS: Wild-type (WT) or ICOS-/- mice were treated intratracheally with 1.0U/kg bleomycin to induce lung injury leading to fibrosis. Lungs were harvested at 3, 5, 7, or 21 days post-treatment and cell infiltrates were analyzed by flow cytometry. Cytokine production was measured by intracellular cytokine staining. Mouse weights and survival were recorded for each experiment and lung fibrosis was determined by hydroxyproline assay.

RESULTS: WT mice expand innate and adaptive ICOS-expressing cells that produce type-2 cytokines in response to bleomycin treatment. Type-2 innate lymphoid cells (ILC2s) that produced IL-5 and IL-13 expanded in the lung on day 3 post-treatment, while IL-13-producing natural killer T cells (NKTs) expanded by day 7. Finally, T helper type 2 cells (Th2s) expanded in the draining lymph node by day 21. Surprisingly, in the absence of ICOS, mice lost significantly more weight in the first week after bleomycin treatment compared to WT mice, and had reduced survival. Importantly, ICOS-deficient mice had defective expansion of ILC2s, NKTs, and Th2s over the course of treatment leading to fewer IL-5+ and IL-13+ cells in the lungs. However, early treatment with recombinant IL-5 and IL-13 was sufficient to protect ICOS-deficient animals from bleomycin-induced weight loss and lung injury.

CONCLUSIONS: Our study demonstrates that early innate type-2 immune responses, driven by ICOS-expressing cells, protect against lung injury. These results imply that low ICOS expression in IPF patients may be a contributing factor to poor recovery from infections and acute exacerbations. Thus, treatment of IPF patients with IL-5 and IL-13 may be a novel therapeutic strategy to protect against lung injury following an acute exacerbation or viral infections.

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SIRT3, the anti-aging major mitochondrial deacetylase, is important for preventing pulmonary fibrosis

AUTHORS: Jablonski, R; Kim, SJ; Cheresh, P; Williams, DB; Morales-Nebreda, L; Yeldandi, A; Pardo, A; Ridge, K; Guis, D; Budinger, GRS; Kamp, D

GENERAL AUDIENCE SUMMARY

OBJECTIVES: Alveolar epithelial cell (AEC) injury from 'exaggerated' lung aging and mitochondrial dysfunction play key roles in the development of lung fibrosis. Our group, using the asbestos lung fibrosis paradigm, has shown that AEC mitochondrial reactive oxygen species (ROS) mediate asbestos-induced AEC mitochondrial DNA (mtDNA) damage and apoptosis by a mitochondrial-regulated death pathway. Sirtuin 3 (SIRT3), the major mitochondrial deacetylase regulating mitochondrial function, mitigates oxidative stress and fibrosis in non-lung models. We reported that SIRT3 deficient (SIRT3-/-) mice have increased lung fibrosis following asbestos exposure associated with exaggerated AEC mtDNA damage and apoptosis. Herein, we determined whether SIRT3 deficiency augments bleomycin-induced fibrosis and whether AEC acetylation is increased in lung biopsy samples from patients with idiopathic pulmonary fibrosis (IPF).

METHODS: Male 8- to 10- week-old 129SJ (SIRT3+/+) and SIRT3-/- mice were treated with a single intratracheal instillation of saline or bleomycin (0.01U). At 3 weeks, the lungs were harvested for endpoints including Sircol collagen assay, fibrosis scoring and measurement of lung compliance. Specimens from explanted lungs of patients with IPF were subject to immunohistochemistry with antibodies to MnSODK68 (a known SIRT3 deacetylation target) and IgG to assess acetylation.

RESULTS: Compared to wild type, Sirt3-/- mice developed increased pulmonary fibrosis following bleomycin exposure as measured by fibrosis score, Sircol assay and lung compliance. Notably, increased acetylation of MnSODK68 was evident in the lungs of patients with IPF. Co-localization studies evaluating MnSODK68/SFPTC are ongoing.

CONCLUSIONS: SIRT3 deficiency enhances bleomycin-induced pulmonary fibrosis in a manner similar to asbestos fibers. An important role for augmented human IPF lung parenchymal cell mitochondrial acetylation is suggested by our pilot studies. Taken together, this suggests that SIRT3 plays a key role in the pathogenesis of IPF in part by preserving AEC mitochondrial function and mtDNA. Given the crucial role for aging in IPF as well as changes in SIRT3 expression with aging, our findings suggest a novel therapeutic target for modulating lung fibrosis.
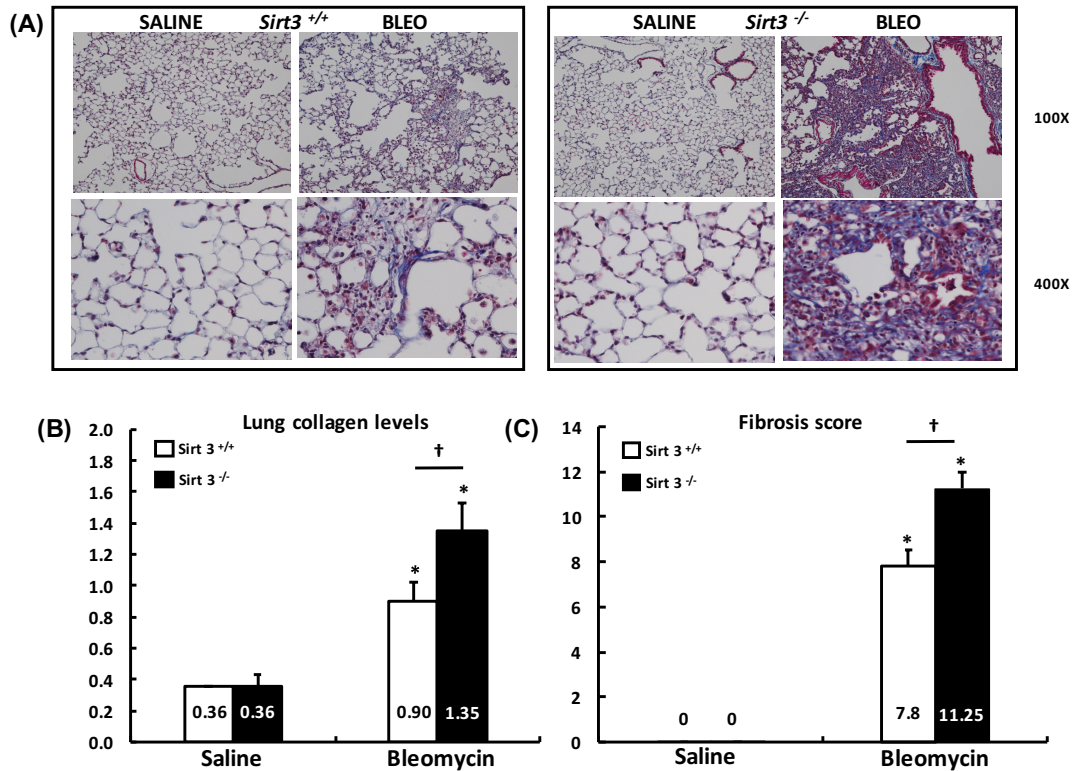
FIGURE 1: SIRT3 deficient mice are more susceptible to bleomycin-induced pulmonary fibrosis.
Three weeks after intratracheal instillation with saline or bleomycin (0.01U), serial mouse lung sections were stained with trichrome stain (A) and scored for fibrosis (C). $n = 1$ for saline/SIRT3+/+, $n = 2$ for saline/SIRT3-/-, $n = 8$ for bleomycin/SIRT3+/+, and $n = 5$ for bleomycin/SIRT3-/-. Whole mouse lungs were treated as described and subject to the Sircol collagen assay (B). $n = 4$ for saline/ SIRT3+/+, $n = 3$ for saline/SIRT3-/-, $n = 5$ for bleomycin/SIRT3+/+, and $n = 4$ for bleomycin/ SIRT3-/-. The values are represented as the mean ± S.E. (*, $p < 0.05$ versus saline. †, $p < 0.05$ versus Sirt3+/+).
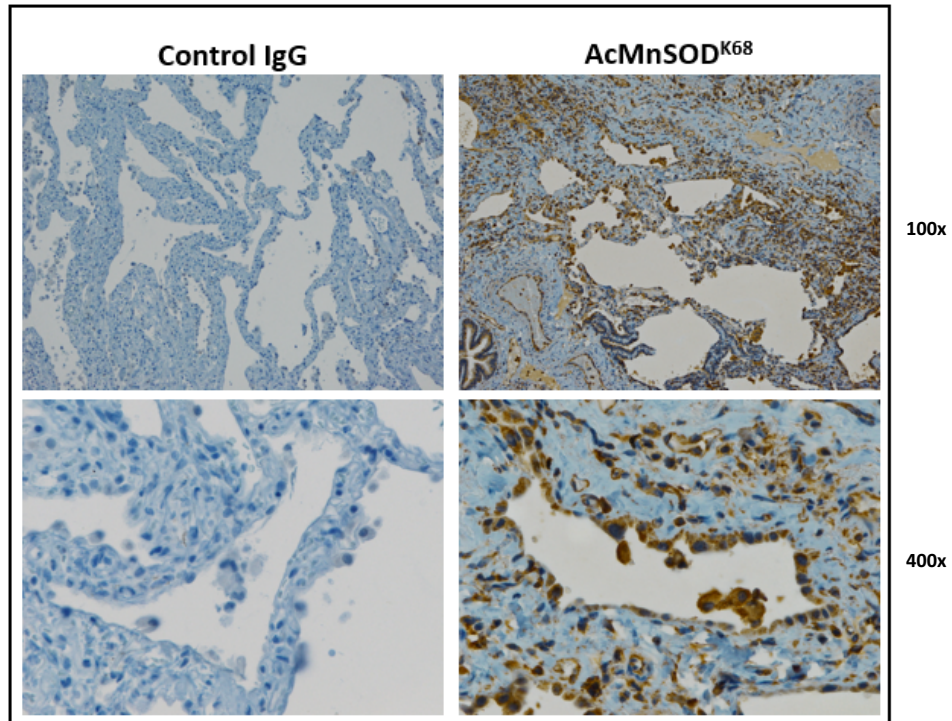
FIGURE 2: Human parenchymal lung cell acetylation is increased in lungs from patients with IPF.
Lung biopsy specimens from patients with IPF were obtained. IHC for anti-AcMnSODK68 shows increased acetylation of lung parenchymal cells as compared to control IgG. $n = 2$ for control IgG, $n = 4$ for AcMnSODK68.

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Evaluating IL-13Ra2 as a Therapeutic Target for Pulmonary Fibrosis

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GENERAL AUDIENCE SUMMARY

Idiopathic pulmonary fibrosis (IPF) is a lethal disease that remains incurable despite recent therapeutic advances. The bronchoalveolar lavage fluid (BALF) of IPF patients shows increased levels of the inflammatory cytokine, IL-17A, suggesting a possible role for Th17-mediated immune responses in IPF. Recently, several groups have shown that Th17 cells express a functional IL-13 receptor, IL-13Ra1, that downregulates the production of IL-17A and upregulates the production of IL-10, suggesting that Th2 cytokines may help regulate Th17-mediated inflammation. Importantly, gene expression studies on lung tissue biopsies of IPF patients have consistently revealed increased expression of an additional IL-13 receptor, IL-13Ra2, that binds IL-13 and sequesters it from the surrounding milieu. We thus hypothesized that IL-13Ra2 may be tempering the IL-13-mediated regulation of Th17 immunity in IPF, and that blocking IL-13Ra2 may provide therapeutic benefit. We examined the role of IL-13Ra2 in pulmonary fibrosis by interrogating the murine IL-17A-driven bleomycin-induced lung injury model. Wild-type (WT) C57BL/6, IL-13Ra2 KO, and IL-10 KO mice were subjected to intratracheal bleomycin injections and were subsequently evaluated for inflammation and fibrosis over a 30-day period. Temporal gene expression analysis in WT mice showed an early increase in IL-13Ra2 expression that was rapidly accompanied by increased expression of IL-17A in the absence of an early Th2 signature. Furthermore, IL-13Ra2 isolated from the BALF of these animals remained unsaturated throughout the 30-day period. Though our studies with IL-13Ra2 KO mice did not show statistically significant changes in fibrosis, gene expression analysis in these mice suggested increased IL-13 effector functions compared to WT mice, supporting the notion that IL-13Ra2 suppresses IL-13 bioactivity. Furthermore, our findings contradict previously published work showing that IL-13Ra2 induces TGFß-mediated fibrosis in the bleomycin model. Given the chronic and progressive nature of IPF, we are now evaluating the role of IL-13Ra2 in a more chronic animal model more closely resembling human disease.

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Long-term efficacy and safety of nintedanib in patients with idiopathic pulmonary fibrosis (IPF)

AUTHORS: Mitchell Kaye; Bruno Crestani; Katy Pelling; Manuel Quaresma; Luca Richeldi

GENERAL AUDIENCE SUMMARY

OBJECTIVE: The INPULSIS® trials assessed the efficacy and safety of nintedanib 150 mg twice daily in patients with IPF. Patients who completed the 52-week treatment period and follow-up visit 4 weeks later could receive open-label nintedanib in an extension trial (INPULSIS®-ON). We assessed the efficacy and safety of nintedanib across INPULSIS® and INPULSIS®-ON.

METHODS: Patients treated with placebo in INPULSIS® initiated treatment with nintedanib in INPULSIS®-ON (placebo/nintedanib); patients treated with nintedanib continued to receive nintedanib. An interim analysis of INPULSIS®-ON was completed after database snapshot in November 2014. Analyses were descriptive.

RESULTS: 1061 patients were treated in INPULSIS® (638 nintedanib, 423 placebo) and 734 in INPULSIS®-ON (430 continuing nintedanib, 304 initiating nintedanib). Mean (SD; minimum–maximum) exposure across INPULSIS® and INPULSIS®-ON was 21.9 (12.0; 0.0–40.6) months for patients treated with nintedanib and 22.4 (11.1; 0.0–40.7) months for patients treated with placebo/nintedanib. For patients treated with nintedanib, mean (SD) change in FVC from baseline to week 52 in INPULSIS® was -89 (264) mL and from the start of INPULSIS®-ON to week 48 of INPULSIS®-ON was -96 (237) mL. For patients treated with placebo in INPULSIS®, mean (SD) change in FVC from baseline to week 52 in INPULSIS® was -203 (293) mL and mean change from the start of nintedanib treatment in INPULSIS®-ON to week 48 of INPULSIS®-ON was -73 (244) mL. The most frequent adverse events reported with nintedanib and placebo/nintedanib in INPULSIS® and INPULSIS®-ON were diarrhea (71.6% and 54.6%), nausea (28.1% and 18.7%) and cough (22.3% and 21.0%). The most frequent serious adverse event was IPF (including disease worsening and acute exacerbations), which was reported in 13.8% of patients treated with nintedanib and 14.7% of patients treated with placebo/nintedanib.

CONCLUSION: An interim analysis of data from INPULSIS®-ON indicated that the effect of nintedanib on slowing disease progression was maintained beyond 52 weeks. The safety and tolerability of nintedanib observed in the INPULSIS® trials were confirmed. Long-term nintedanib treatment (up to 40 months) had an acceptable safety and tolerability profile.

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· 91

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miRNAs that regulate LDHA inhibit TGF induced myofibroblast differentiation

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GENERAL AUDIENCE SUMMARY

OBJECTIVES: We previously identified that lactate dehydrogenase A (LDHA) overexpression in human lung fibroblasts induces myofibroblast via an increase in the rate of extracellular acidification and subsequent activation of TGF-beta. We have also shown that LDHA expression is induced by TGF-beta thus contributing to a pro-fibrotic feed forward loop. We have recently identified that several miRNAs that regulate LDHA expression are decrease in IPPF. We hypothesize the regulation of these miRNAs may be one of the mechanisms by which TGF-beta induces LDHA expression and myofibroblast differentiation in primary human lung fibroblasts.

METHODS: We first identified the miRNAs that target LDHA and were differentially expressed in a previously published IPF miRNA expression profile compared to a control group. Primary human lung fibroblasts were then cultured with and without TGF-beta. miRNA profiles in the fibroblast were then examined. Lastly, fibroblasts were cultured with and without TGF-beta and/or a miRNA mimic after which LDHA and aSMA expression were evaluated by Western blot and extracellular acidification rates were measured using a seahorse bioassay.

RESULTS: We identified that there is a three-fold decrease in miR-338-3p and a two-fold decrease in miR-30d in the IPF miRNA profile compared to the control profile. The expression of both of these miRNAs was significantly decreased in primary lung fibroblasts after treated with TGF-beta. Lastly, a miR-338-3p mimic inhibited TGF-beta induced LDHA expression and aSMA expression and inhibited the increase in extracellular acidification induced by TGF-beta.

CONCLUSIONS: We have identified several miRNAs that regulate LDHA expression and are differentially expressed in IPF. Furthermore, treatment with a mimic of miR-338-3p inhibits TGF-beta induced LDHA expression and extracellular acidification suggesting that miRNAs that target LDHA may represent novel anti-TGF therapy.

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Rare variants in RTEL1 are associated with pulmonary fibrosis

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GENERAL AUDIENCE SUMMARY

OBJECTIVE: Since the genetic basis of familial interstitial pneumonia (FIP) remains uncertain in a majority of families, we performed whole-exome sequencing (WES) of affected individuals with FIP with the goal of identifying new disease-causing rare genetic variants.

METHODS: Affected subjects from 25 families were initially selected from our FIP registry for WES from genomic DNA. Candidate rare variants were confirmed by Sanger sequencing and co-segregation analysis was performed in families, followed by additional sequencing of affected individuals from another 165 kindreds. Telomere length was measured by southern blot. EBV-immortalized lymphocytes from RTEL1 rare carriers and controls, as well as A549 cells transfected with wild type (WT) or mutant RTEL1, were exposed to radiation or bleomycin to analyze DNA-damage responses. DNA damage quantified by single cell electrophoresis (COMET) assay or H2AX staining by flow cytometry. Cell proliferation was quantified by brdU incorporation.

RESULTS: By analysis of WES data, we identified a potentially damaging rare variant in RTEL1 that segregated with disease in one of the 25 families from the initial cohort and was associated with short telomeres in peripheral blood mononuclear cells (1st percentile for age). Evaluation of additional families revealed another 7 families (4%) with heterozygous rare variants in RTEL1 that segregated with clinical FIP. Probands and unaffected carriers of these rare variants had short telomeres (<10% for age) in peripheral blood mononuclear cells and increased T-circle formation, indicating impaired RTEL1 function. EBV-immortalized lymphocytes from RTEL1 RV carriers showed delayed repair of DNA damage as well as progressive telomere shortening through successive passages, in contrast to control lymphocytes which lengthened telomeres over time. While overexpression of WT RTEL1 in A549 cells enhanced repair from bleomycin or radiation-induced DNA damage, overexpression of mutant RTEL1 failed to show protection. In addition, A549 cells expressing mutant RTEL1 exhibited increased p53 expression and impaired cellular proliferation.

CONCLUSIONS: Rare loss-of-function variants in RTEL1 represent a newly defined genetic cause of FIP. RTEL1 RVs are associated with altered DNA dama

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A Bundle of Care Improves Outcomes in Idiopathic Pulmonary Fibrosis

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Victor J. Thannickal MD, Joao A. de Andrade MD

GENERAL AUDIENCE SUMMARY

OBJECTIVES: Idiopathic pulmonary fibrosis (IPF) is a chronic lung disease with poor prognosis and limited treatment options. The 2011 ATS IPF Guidelines recommends a number of interventions, however the impact of adherence to such measures on outcomes is unknown. Our hypothesis is that patients with higher adherence to a bundle of care (BOC) based on these guidelines would have better outcomes compared to those with low adherence.

METHODS: We conducted a retrospective cohort study and enrolled patients diagnosed with IPF at UAB from 2000 to 2013. We excluded patients with fewer than three visits to UAB and those with combined IPF and emphysema. The primary outcome measure was transplant-free survival. The BOC components are: 1) visits to a specialized Interstitial Lung Diseases clinic with evaluation of PFTs at least twice in 12 months; 2) yearly referral to pulmonary rehabilitation; 3) yearly 6-minute walk test; 4) yearly echocardiogram; and 5) continuous anti gastroesophageal reflux therapy. Each fulfilled component was attributed a score of "1" per year of follow up and a mean score for each component was calculated based on the number of years of follow up. The maximum adherence score was 5. Cox proportional hazards model was used to study the association between adherence score and transplant-free survival.

RESULTS: We enrolled 284 subjects. 94% were Caucasian, 69% were male, and 71% were either current or past smokers. The mean age at diagnosis was 65.3 and mean BMI was 30.6. The mean %FVC at initial visit was 63% and mean %DLCO was 45%. The median survival was 17.9 months. Age, gender, smoking status, BMI, %FVC, %DLCO did not differ between quintiles of the adherence score. Lower adherence to BOC (score =1) was associated with a lower transplant-free survival time compared to patients with higher adherence to BOC (score >4) (HR 2.27, CI 1.12- 4.64, p=0.02).

CONCLUSION: IPF patients with higher adherence to the BOC had longer transplant-free survival compared to those with low adherence. These findings need prospective validation.
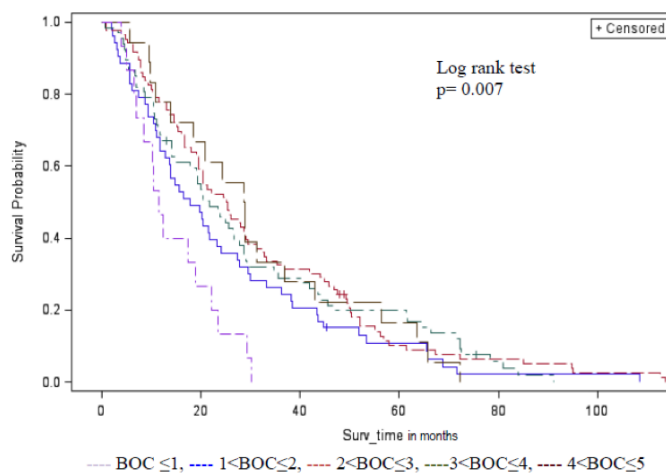
Figure 1: BOC score and transplant free survival

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95

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Safety of pirfenidone in patients with idiopathic pulmonary fibrosis (IPF): Integrated analysis of cumulative data from 5 clinical trials

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GENERAL AUDIENCE SUMMARY

OBJECTIVES: IPF is a chronic, progressive and irreversible disease that requires long-term clinical management. To further evaluate the clinical safety of pirfenidone in patients with IPF, we performed a comprehensive integrated analysis of safety data from 5 clinical trials.

METHODS: All patients assigned to receive pirfenidone (2403 mg/d) in the Phase 3 ASCEND (Study 016) and CAPACITY (Studies 004/006) trials and all patients receiving >=1 dose of pirfenidone in either of two ongoing open-label studies (Studies 002 and 012) comprised the integrated population. Study 002 is a compassionate use study in the U.S.; RECAP (Study 012) is evaluating pirfenidone in patients who completed one of the Phase 3 studies. Analyses were based on the January 15, 2014 interim data cut.

RESULTS: 1299 patients were included in the integrated population. The cumulative total exposure to pirfenidone was 3160 person exposure years (PEY). The median duration of exposure was 1.7 years (range, 1 week–9.9 years); 545 (42%) patients received pirfenidone for >=2 years and 325 (25%) patients received pirfenidone for >=4 years. The majority of patients (75.8%) received a mean daily dose of >=1800 mg. Consistent with prior observations, gastrointestinal and skin-related events were among the most common treatment emergent adverse events (Table); these were almost always mild to moderate in severity, reversible with dose modification and rarely led to treatment discontinuation. Cough, dyspnoea and IPF were the most common respiratory adverse events in the integrated population — a finding that is consistent with expectations in patients with a chronic progressive respiratory disease followed over a long period of observation. Aminotransferase (ALT or AST) elevations (>3 x ULN) occurred in 40/1299 (3.0%) patients in the integrated population.

CONCLUSIONS: A comprehensive integrated analysis of safety outcomes in a large, well-defined cohort of 1299 patients with IPF who were treated with pirfenidone for up to 9.9 years demonstrated that treatment with pirfenidone is safe and generally well tolerated. These observations provide further evidence to support the long-term clinical safety of pirfenidone in patients with IPF.

Table. Treatment emergent adverse events in the integrated population compared with the pooled pirfenidone 2403 mg/d and placebo groups in the Phase 3 trials*

	Integrated Population (N=1299)†
Median (range) duration of exposure, yr	1.7 (>0, 9.9)
Treatment emergent adverse event, %	
Nausea	37.6
Cough	35.1
Dyspnea	30.9
Upper respiratory tract infection	30.6
Idiopathic pulmonary fibrosis	29.3
Fatigue	28.2
Diarrhea	28.1
Rash	25.0
Bronchitis	23.8
Headache	21.6
Nasopharyngitis	21.3
Dizziness	21.2
Dyspepsia	18.4
Vomiting	15.9
Weight decreased	15.6
Back pain	15.4
Anorexia	15.2

*Occurring in ≥15% of patients in the cumulative clinical database.
†Includes 2 patients in Study 002 with a diagnosis of "pulmonary fibrosis."

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97

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Next Generation Sequencing Does Not Support a Causative Role for Herpes Viruses in IPF

AUTHORS: Joseph Lasky, Qinyan Yin, Erik Flemington, Dongxiao Zhu, Naftali Kaminski,
Joao de Andrade

GENERAL AUDIENCE SUMMARY

RNA-seq analysis does not substantiate a causative link between herpes virus infection and IPF

There are several publications showing an association between herpes virus infection and idiopathic pulmonary fibrosis (IPF). These reports use immunohistochemistry and/or PCR, which are susceptible to specificity artifacts. Thus, we investigated the possible association between IPF and viral RNA expression using next-generation sequencing, which has the potential to provide both a high degree of sensitivity as well as specificity. We quantified viral RNA expression for 740 viruses in 21 IPF patient lung biopsy samples and 17 age-matched controls. Our RNA-seq results were confirmed using Real-time RT-PCR for select viruses (EBV, herpes Saimiri and HERV-k). HERV-k expression was examined because of reports indicating that it is elevated in other fibrotic diseases, and because conceptually HERV-k could promote fibrogenesis by inducing cellular stress. Moreover, HERV-k expression is reported to be enhanced in response to herpes virus infection. Although we identified sporadic low-level evidence of viral infections in our lung tissue samples, we did not find a statistical difference for expression of any virus, including HERV-k, between IPF and control lungs. To our knowledge, this is the first report that employs RNA-seq to assess whether or not viral infections are linked to IPF. Our results do not address the role of viral infection in the so-called acute exacerbation of IPF, however, they do not support a causative connection between herpes virus infection and IPF.

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Predictors of Mortality Do Not Predict Disease Progression in Idiopathic Pulmonary Fibrosis

AUTHORS: Brett Ley; Williamson Z. Bradford, Eric Vittinghoff, Derek Weycker, Roland M. du Bois, Harold R. Collard

GENERAL AUDIENCE SUMMARY

OBJECTIVES: Mortality prediction is well studied in idiopathic pulmonary fibrosis (IPF), but little is known about predictors of pre-mortality disease progression. Identification of patients at risk for disease progression would be useful for clinical decision-making and designing clinical trials. The objective of this study was to determine whether commonly measured clinical characteristics of patients with IPF could be used to accurately predict risk of future disease progression.

METHODS: In a large clinical trial cohort of IPF patients (n=1113), we comprehensively screened multivariate models of candidate baseline and past-change predictors for disease progression defined by 48-week worsening of forced vital capacity (FVC), dyspnea (UCSD-SOBQ), six-minute walk distance (6MWD), and occurrence of respiratory hospitalization. Progression outcomes were modeled as appropriate, by slope change using linear regression models, binary change using logistic regression models, and time-to-respiratory hospitalization using competing risks models.

RESULTS: The overall cohort experienced considerable disease progression. However, top-performing models did not meaningfully predict most measures of disease progression. For example, prediction modeling explained = 1% of the observed 48-week slope change in FVC, UCSD-SOBQ, and 6MWD (cross-validated R2 values = 0.01). Models performed better for binary measures of disease progression (e.g. =10% decline in FVC), but were still largely inaccurate (cross-validated c statistic = 0.61 for = 10% decline in FVC, =0.67 for = 10% decline in FVC or death, = 0.66 for = 20 unit increase in UCSD-SOBQ, = 0.73 for = 100m decline in 6MWD, and = 0.64 for respiratory hospitalization).

CONCLUSIONS: Clinical prediction models poorly predicted disease progression by multiple measures in IPF. This is in contrast to mortality prediction, and has implications for clinical practice and research.

Table. Measures of predictiveness for the top performing prediction models

Disease Progression Measure	Top model components	Linear models CV-R^2	Logistic models CV-c statistic
FVC, % predicted			
Absolute slope	Age + FVC + SOBQ + Δ6MWD + Male	0.0096	
Relative slope	BMI + FEV1:FVC + FVC + SOBQ + WSPO2 + Δ6MWD + ΔDLco + O2 Use	0.0037	
Absolute slope (not imputed)*	6MWD + DLco + Δ6MWD + ΔDLco + ΔFVC + Male + RH + ΔSOBQ	0.0395	
Absolute slope (imputed)*	DLco + ΔFVC + O2 Use	0.0148	
≥10% absolute decline	FEV1:FVC + FVC + WSPO2 + ΔFVC + O2 Use + RH + ΔSOBQ		0.605
≥10% absolute decline or death	BMI + 6MWD + FEV1:FVC + FVC + SOBQ + WSPO2 + Male + RH		0.667
≥10% sustained absolute decline	FEV1:FVC + FVC + SOBQ + WSPO2 + ΔFVC + Male + RH + ΔSOBQ		0.642
≥10% relative decline	6MWD + DLco + FEV1:FVC + FVC + ΔFVC + Male + ΔSOBQ		0.614
UCSD-SOBQ			
Slope	WSPO2 + ΔDLco + Male + ΔSOBQ	0.0043	
≥5 unit increase	Age + 6MWD + FVC + WSPO2 + Δ6MWD + Male + RH + ΔSOBQ		0.637
≥20 unit increase	BMI + 6MWD + FEV1:FVC + FVC + WSPO2 + ΔDLco + RH + ΔSOBQ		0.663
6MWD			
Slope	Age + 6MWD + WSPO2 + Δ6MWD + ΔDLco + Male + O2 Use	0.0023	
≥50 m decline	6MWD + FVC + SOBQ + WSPO2 + Δ6MWD + RH		0.695
≥100 m decline	6MWD + DLco + FVC + SOBQ + WSPO2 + Δ6MWD + ΔDLco + O2 Use		0.730
Respiratory Hospitalization	BMI + WSPO2 + ΔFVC + RH		0.636

*Imputed values were available for the CAPACITY trials only (n = 329)

Abbreviations: CV = cross-validated; FVC = forced vital capacity, UCSD-SOBQ or SOBQ = University of California San Diego Shortness of breath questionnaire, Δ = prior 24-week change, 6MWD = six-minute walk distance, BMI = body-mass index, DLCO = diffusing capacity of the lung for carbon monoxide, O2 = oxygen, WSPO2 = lowest saturation on six-minute walk test, FEV1:FVC = ratio of forced expiratory volume in 1 second to forced vital capacity, RH = respiratory hospitalization in the prior 24 weeks

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Exploring the Understanding of and Preparedness for the Palliative Care Experience of Idiopathic Pulmonary Fibrosis (IPF)

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GENERAL AUDIENCE SUMMARY

OBJECTIVE: We observed that palliative care referral and initiation of discussions regarding end-of-life (EOL) planning for patients with IPF often occurred late in the disease course. A study conducted in our setting confirmed that patients with IPF were referred to the University of Pittsburgh Simmons Center for Interstitial Lung Disease (ILD) late in their disease (median referral was 2 years after diagnosis), many died (57%) in a hospital setting, frequently in the intensive care unit (ICU), and few (14%) receive a formal referral to palliative care, often late in their disease [1]. Best strategies to change this outcome are unclear. The purpose of this pilot study was to identify ways to promote earlier use of palliative care by questioning patients & caregivers about their understanding of the disease and management.

METHODS: Three separate focus groups (5 current patients with IPF, 5 family caregivers of current patients and 3 family caregivers of decedent IPF patients) were conducted. Group discussion was led by a facilitator not associated with patient care using predetermined questions and open-ended probes.

RESULTS: Coding was carried out by personnel in the Qualitative Data Analysis Program at the University of Pittsburgh. A thematic analysis (2, 3) was used to develop a codebook that identified major conceptual categories. Several predominant themes were identified, including: (1) IPF knowledge gap; i.e.: lack of education materials, (2) uniqueness of the IPF experience and (3) barriers to using supplemental oxygen. Patient/caregiver comments reflected need for greater knowledge about the disease, despite provision during clinic visits. Caregivers, universally, wanted to only hear hopeful comments. Oxygen was viewed as a sign of decline and therefore a source of frustration.

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101

CONCLUSIONS: Clinicians need to provide disease information that includes information about disease progression, the benefits of palliative care in ameliorating symptom burden and addressing advanced care planning. Interactive, tailored early palliative care resources may be a way to introduce this information in a setting that encourages discussion and sharing of experiences.

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Equilibrative nucleoside transporter down-regulation exacerbates bleomycin induced pulmonary fibrosis

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GENERAL AUDIENCE SUMMARY

OBJECTIVES: Idiopathic pulmonary fibrosis (IPF) is a devastating lung disease responsible for up to 30,000 deaths per year in the U.S., with limited treatment available. Adenosine is a nucleoside produced in response to injury; an increased extracellular adenosine level, which is actively regulated by equilibrative nucleoside transporters (ENTs), is associated with pulmonary fibrosis. The purpose of this study is to investigate the role of ENTs in IPF. Specifically, we hypothesize that ENT down-regulation contributes to elevated extracellular adenosine levels and therefore exacerbates pulmonary fibrosis.

METHODS: Male wild type and ENT1 and ENT2 knockout mice (C57BL/6 background) were exposed to bleomycin to induce lung fibrosis. ENT expression was examined in human lung samples from IPF and control patients. Furthermore, in vitro experiments using human and mouse lung epithelial cells were conducted to identify potential mechanisms of ENT down-regulation. Protein, mRNA and adenosine levels were evaluated using RT-qPCR, western blot, immunohisto-chemistry staining and high performance liquid chromatography (HPLC).

RESULTS: ENT1 and ENT2 expression were diminished in the epithelial cells of human IPF lungs compared with controls. ENT1 and ENT2 expression were also inhibited by bleomycin and consistent with adenosine levels in bronchoalveolar lavage fluid (BALF) and fibrosis progression. In vivo experiments indicated that bleomycin induced more severe lung fibrosis in ENT1 and ENT2 knockout mice. The exacerbation of lung fibrosis was in accordance with an elevation of lymphocytes and interleukin-6 (IL-6) in BALF. Bleomycin failed to inhibit ENT1 and ENT2 expression in IL-6 knockout mice. In vitro studies revealed that IL-6 inhibited ENT expression in human and mouse epithelial cells by phosphorylation of STAT3. MicroRNA-124 and microRNA 17-92 cluster may play important roles in regulating ENT1 and ENT2 expression.

CONCLUSIONS: IL-6 mediated ENT down-regulation contributes to elevated extracellular adenosine levels and exacerbation of pulmonary fibrosis. Therefore, modulating IL-6 signaling in ENT inhibition may be a key mechanism for future IPF treatment.

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Prevalence and determinants of frailty in fibrotic interstitial lung disease

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GENERAL AUDIENCE SUMMARY

OBJECTIVES: Frailty is defined as the accumulation of deficits that decrease the ability to respond to biological stress. Patients with fibrotic interstitial lung disease (ILD) have a high risk of frailty due to direct consequences of ILD as well as age, comorbid diseases, and adverse effects of pharmacotherapies. The objective of this study was to examine the prevalence and determinants of frailty in ILD.

METHODS: Patients with fibrotic ILD were recruited from a specialized ILD clinic. Patients with ILD secondary to a systemic disease (e.g. connective tissue disease) were excluded. Frailty was determined using the Frailty Index, an established method for measuring frailty that is based on the presence or absence of multiple deficits, including comorbidities, symptoms, and functional limitations(1). The Frailty Index was calculated based on the proportion of deficits present, with frailty defined as a score >0.21 (i.e. presence of >21% of surveyed deficits). Dyspnea was measured using the University of California San Diego Shortness of Breath Questionnaire. The relationship of frailty with potential predictors was tested and multivariate analysis was conducted to determine independent predictors of frailty.

RESULTS: The study included 74 patients (27 with idiopathic pulmonary fibrosis [IPF]). Mean age was 67 years, 58% were men, mean FVC was 75%, and mean DLCO was 51%. The definition of frailty was met in 43% of the cohort (41% in IPF). The frequency of responses to each component of the Frailty Index is shown in Figure 1. Frailty was associated with FEV1 (r=-0.27;p=0.02), DLCO (r=-0.26;p=0.03), ILD-GAP Index (r=0.33;p=0.006), time since diagnosis (r=0.23;p=0.05) and dyspnea score (r=0.66;p<0.00005; Figure 2). Age, sex, smoking history and body mass index were not associated with frailty. Dyspnea severity was the only independent predictor of the Frailty Index (0.038 increase in Frailty Index for every 10 point increase in dyspnea score; R-squared=0.40;p<0.00005).

CONCLUSIONS: Frailty is associated with multiple measures of disease severity in fibrotic ILD. Dyspnea severity was the only independent predictor of frailty in fibrotic ILD, demonstrating that dyspnea is a more important determinant of frailty than objective measures of pulmonary function.

Figure 1. Percentage of fibrotic ILD patients with each component of frailty.

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105
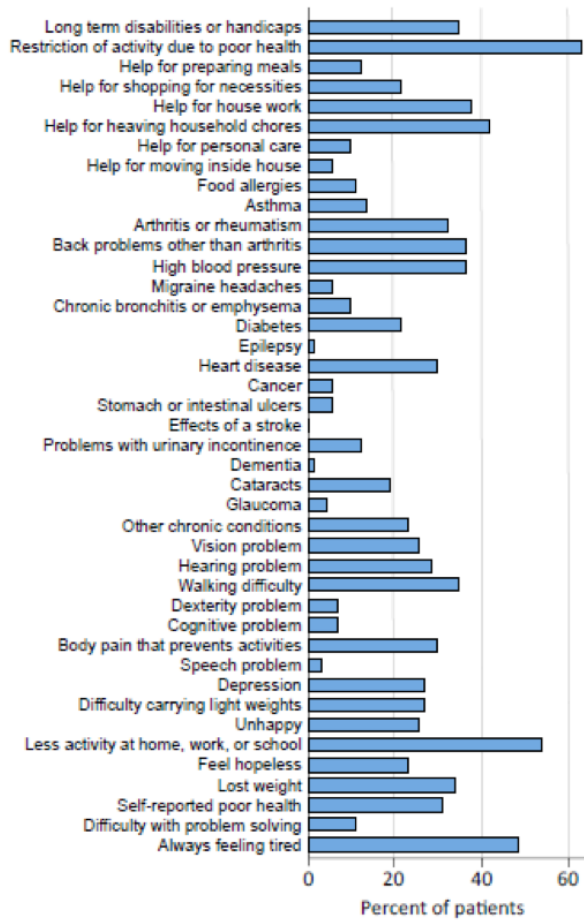
Figure 2. Association of Frailty Index with dyspnea severity.
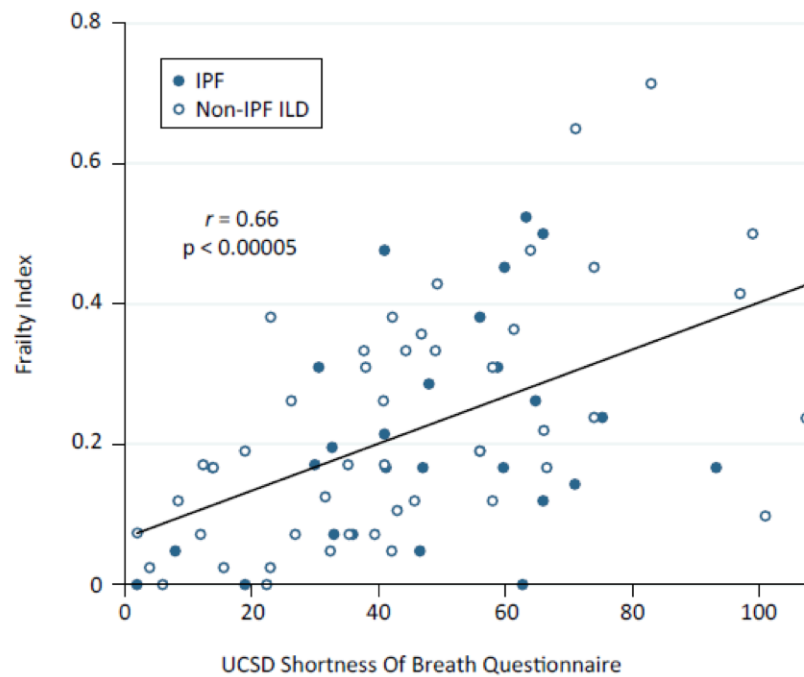
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Development of a standardised education program for patients with interstitial lung disease: a qualitative study

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GENERAL AUDIENCE SUMMARY

OBJECTIVES: Pulmonary rehabilitation (PR) improves exercise tolerance, quality of life and dyspnea in patients with interstitial lung disease (ILD). However, the impact of education and behaviour change on outcome has not been explored in these patients. The goals of this qualitative study were to assess ILD patients' satisfaction about the education they receive during routine medical care, identify themes and educational topics patients and healthcare professionals believe should be included in PR and develop a structured conceptual framework of the main components of an educational program for patients with ILD.

METHODS: Four focus groups with ILD patients and 10 semi-structured interviews with health care professionals with an expertise in ILD and/or PR were conducted in 2 academic centers (University of California, San Francisco and Centre Hospitalier de l'Université de Montréal). Focus group included 24 patients: 12 with a diagnosis of idiopathic pulmonary fibrosis (IPF), 4 with hypersensitivity pneumonitis, 5 with a connective tissue disease (CTD) related-ILD and 3 with other ILD diagnosis. Four nurses, 2 kinesiologists and 4 physicians participated in the healthcare professional interviews.

RESULTS: Patients unanimously expressed dissatisfaction about the education they received within their medical care. A majority of them sought for additional information and education material, mostly using the Internet, but felt the available content did not completely fulfill their knowledge gap. Patients and caregivers identified key topics they felt should be included in a ILD specific program: disease education, benefits of exercising, dealing with symptoms of anxiety and depression, end of life and palliative care and determinants of disease including change of behavior and self-management.

CONCLUSIONS: This study provides a better understanding of the needs of patients and caregivers regarding education of patients with ILD. It lays the foundations for the development of a structured educational program. Adding a tailored education program to PR for patients with ILD seems a promising way to deliver more information and meet patient's wish for additional knowledge.

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Effect of continued treatment with pirfenidone following a clinically meaningful decline in percent predicted forced vital capacity in patients with idiopathic pulmonary fibrosis (IPF)

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GENERAL AUDIENCE SUMMARY

OBJECTIVES: The clinical course in patients with IPF is characterized by substantial inter- and intra-subject variability in the rates of disease progression, thereby confounding clinical assessments of therapeutic responses in individual patients. We pooled data from three Phase 3 trials to assess the potential benefit of continued treatment with pirfenidone in patients who experienced a $>=10\%$ decline in percent predicted forced vital capacity (%FVC) during the first 6 months of treatment.

METHODS: Source data included all patients randomized to treatment with pirfenidone 2403 mg/d or placebo in the Phase 3 ASCEND or CAPACITY studies (N=1247). We selected patients with a >=10% absolute decline in %FVC by the month 3 or 6 study visit and compared the proportion of patients in the pirfenidone and placebo groups who experienced any of the following during the subsequent 6-month interval: (1) >=10% absolute decline in %FVC or death; (2) no further decline in %FVC; or (3) death. Observed data were used in the analysis.

RESULTS: 34 (5.5%) and 68 (10.9%) patients in the pooled pirfenidone and placebo groups, respectively, experienced a >=10% absolute decline in %FVC between baseline and month 6 (relative difference, 49.5%). Analysis of outcomes during the subsequent 6-month interval demonstrated that fewer patients in the pirfenidone group compared with placebo experienced a >=10% decline in %FVC or death (pirfenidone, 2/34 [5.9%] vs. placebo, 19/68 [27.9%]). More patients in the pirfenidone group compared with placebo had no further decline in %FVC (20/34 [58.8%] vs. 26/68 [38.2%]; Table). Additionally, there were fewer deaths in the pirfenidone group (1/34 [2.9%]) compared with placebo (14/68 [20.6%]).

CONCLUSIONS: Among patients who experienced a >=10% decline in %FVC during the first 6 months of treatment, continued treatment with pirfenidone resulted in a lower risk of %FVC decline or death during the subsequent 6 months. These findings suggest a potential benefit to continued treatment with pirfenidone despite an initial decline in FVC.

Table. Outcomes during the 6-month period following an initial decline in percent predicted FVC ≥10% during the first 6 months of treatment

Outcome, n (%)	Pirfenidone (n=34)	Placebo (n=68)	Relative Difference*	P Value[†]
≥10% decline in FVC or death	2 (5.9)	19 (27.9)	−78.9%	0.009
Death	1 (2.9)	14 (20.6)	−85.7%	0.018
>0% to <10% decline in FVC	12 (35.3)	23 (33.8)	4.3%	ND
No further decline in FVC[‡]	20 (58.8)	26 (38.2)	53.8%	0.059

FVC=forced vital capacity.
*Relative difference calculated using the following formula: 100 × [pirfenidone - placebo]/[placebo].
[†]Fisher's exact test.
[‡]Either no decline or an increase in FVC.

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.... 109

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Safety and tolerability of nintedanib in patients with idiopathic pulmonary fibrosis (IPF): data from post-marketing surveillance in the United States

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GENERAL AUDIENCE SUMMARY

OBJECTIVES: The efficacy and safety of nintedanib 150 mg twice daily were assessed in the two replicate, 52-week, placebo-controlled INPULSIS® trials. In both trials, nintedanib significantly reduced the annual rate of decline in forced vital capacity compared with placebo and had a side-effect profile that was manageable for most patients. Nintedanib was approved for the treatment of IPF in the US in October 2014. Post-marketing surveillance was conducted to obtain additional information on the safety and tolerability of nintedanib in the real-world clinical setting in the US.

METHODS: Data were collected from the drug safety database from the time of drug launch (15 October 2014) to database lock on 31 May 2015. Data on adverse events in patients treated with nintedanib were collected both via proactive patient communications, as part of a patient support program, and by the spontaneous reporting system. Adverse events were coded according to preferred terms in the Medical Dictionary for Regulatory Activities. Serious adverse events were defined according to International Conference on Harmonization criteria as adverse events that were fatal or life threatening, required or prolonged hospitalization, were associated with a congenital anomaly, or resulted in a disability.

RESULTS: At the time of database lock, 3838 patients had been treated with nintedanib. Duration of exposure to nintedanib ranged from 14 to 265 days with a mean exposure of 88 days. Total duration of exposure to nintedanib was 924 patient-years. The 15 most frequently reported adverse events are presented in the figure below. Diarrhea was the most frequently reported adverse event.

CONCLUSION: First data from post-marketing surveillance in the US were consistent with the safety profile of nintedanib as described in the label. Treatment with nintedanib in the real-world clinical setting appeared to have an acceptable safety and tolerability profile, with no new safety concerns identified.

Figure
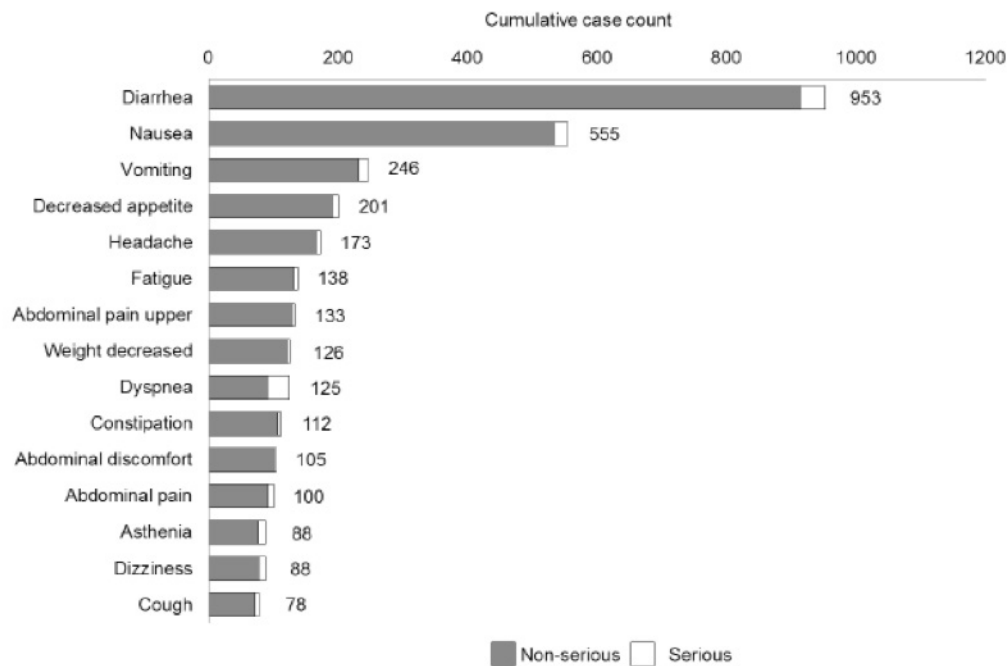
Adverse events presented by MedDRA preferred term

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TOLLIP, MUC5B and the Response to N-acetylcysteine among Individuals with Idiopathic Pulmonary Fibrosis

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3 Duke Clinical Research Institute; Duke University
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5 Department of Medicine; The University of Colorado

GENERAL AUDIENCE SUMMARY

OBJECTIVE: Idiopathic pulmonary fibrosis (IPF) is a devastating lung disease of unknown etiology. TOLLIP and MUC5B play important roles in lung host defense, an immune process influenced by oxidative signaling. Whether polymorphisms in TOLLIP and MUC5B modify the effect of immunosuppressant and antioxidant therapy in patients with IPF is unknown. In this investigation we determine whether single nucleotide polymorphisms (SNPs) within TOLLIP and MUC5B modify the effect of trial interventions in patients participating in the PANTHER-IPF clinical trial.

METHODS: SNPs within TOLLIP (rs5743890/rs5743894/rs5743854/rs3750920) and MUC5B (rs35705950) were genotyped. Interaction modeling was conducted using multivariable Cox regression followed by genotype-stratified survival analysis using a composite endpoint of death, transplant, hospitalization or =10% FVC decline.

RESULTS: Significant interaction was observed between NAC therapy and rs3750920 within TOLLIP ($p_{interaction}$ = 0.001). After stratifying by rs3750920 genotype, NAC therapy was associated with a significant reduction in composite endpoint risk (HR 0.14; 95% CI 0.02-0.83; p=0.03) in those with a TT genotype, but a non-significant increase in composite endpoint risk (HR 3.23; 95% CI 0.79-13.16; p=0.10) in those with a CC genotype. These findings were then replicated in an independent IPF cohort.

CONCLUSIONS: NAC may be an efficacious therapy for IPF patients with an rs3750920 (TOLLIP) TT genotype. Conversely, NAC therapy was associated with a trend towards harm in those with a CC genotype. A genotype-stratified prospective clinical trial should be conducted prior to any recommendation regarding the use of off-label NAC to treat IPF.

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Classifying Unclassifiable Interstitial Lung Disease

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GENERAL AUDIENCE SUMMARY

OBJECTIVES: Despite multidisciplinary review of clinical, radiographic, and pathologic data, a significant number of cases of interstitial lung disease (ILD) remain unclassifiable. Unclassifiable ILD has been associated with a worse prognosis than connective tissue disease-ILD or hypersensitivity pneumonitis. However, the characteristics of patients with unclassifiable ILD are unknown. We aim to: (1) qualify the categorical reasons why a specific diagnosis cannot be rendered, and (2) compare the features of unclassifiable ILD with IPF.

METHODS: We performed a prospective cohort study of patients with ILD evaluated at the University of Pennsylvania's Harron Lung Center between July 2007 and July 2015. Enrolled subjects underwent a detailed history and physical, CT imaging, and pulmonary function testing at their initial evaluation. Utilizing published criteria, diagnoses were established by a multidisciplinary consensus review including pulmonologists expert in ILD, a thoracic radiologist and a pulmonary pathologist.

RESULTS: A total of 282 subjects were evaluated, of which 59 (21%) were diagnosed with unclassifiable ILD. The clinical features of subjects with unclassifiable ILD are detailed in Table 1. We identified three categories of unclassifiable ILD: 58% of subjects had disease features not meeting criteria for a specific ILD; 28% had reticulations without honeycombing, consistent with possible usual interstitial pneumonia (UIP) according to the ATS statement on IPF; in 12%, a consensus diagnosis could not be reached due to discrepant data or competing diagnoses. While not meeting criteria for a connective tissue disease, 28% of subjects had a positive serology screen. Most subjects with unclassifiable ILD had fibrotic features. For subjects with UIP-like reticulations, only 24% demonstrated progression to UIP on follow-up imaging at least one year later.

CONCLUSIONS: We identified three discrete categories of unclassifiable ILD. Failure to fulfill criteria for a specific ILD was the largest category. Whether the subgroup of UIP-like reticulations represents an early or more benign phenotype of IPF remains to be established. Longer-term outcomes of unclassifiable ILD are a future focus of our group.

Table 1 Clinical features of unclassifiable ILD

	Unclassifiable ILD n = 59
Age at disease onset	64.4 (11.6)
Male gender	32 (54%)
Ancestry	
African American	9 (15%)
Caucasian	47 (80%)
Other	4 (6%)
Smoking history	
Current	2 (3%)
Former	35 (59%)
Positive serology screen	
RF or CCP	8 (14%)
ANA	8 (14%)
Other	1 (2%)
FVC, % predicted	69 ± 18%
DLCO, % predicted	56 ± 22%
Surgical lung biopsy	10 (17%)
Category of unclassifiable ILD	
Non-specific clinical features[i]	35 (59%)
UIP-like reticulations[ii]	17 (29%)
No consensus/discordant data	7 (12%)
Follow-up data[iii]	
> 10% decline in FVC	12 (60%) n=20
Progression to radiographic UIP	5 (18%) (n=28)

RF rheumatoid factor, CCP anticyclic citrullinated peptide, ANA antinuclear antibody, FVC forced vital capacity, DLCO carbon monoxide diffusing capacity

Data given as mean ± standard deviation, or n (%)

[i] Non-specific features included CT abnormalities inconsistent with UIP or sarcoidosis, in patients without a connective tissue disease and not meeting criteria for hypersensitivity pneumonitis.

[ii] Peripheral and basilar predominant reticulations without honeycombing

[iii] At least one year after initial testing at disease presentation

Table 2 Fibrotic unclassifiable ILD and IPF

	Unclassifiable: Non-specific features n = 35	Unclassifiable: Discrepant data n = 7	Unclassifiable: UIP-type reticulations n = 17	IPF n = 57	p-value
Age at disease onset	63.0 ±13.2	59.3 ± 11	69.1 ± 6.5	66.7 ± 7.5	0.047
Male gender	18 (51%)	2 (29%)	11 (65%)	42 (74%)	0.087
Ancestry					
African ancestry	7 (20%)	2 (29%)	0	2 (3.5%)	
Caucasian	24 (69%)	5 (71%)	17 (100%)	51 (89%)	0.04
Other	4 (11%)	0	0	5 (9%)	
Smoking history	22 (63%)	4 (57%)	11 (65%)	40 (70%)	0.87
FVC, % predicted	64.6 ± 18	67.7 ± 14.5	78.6±16.4	68.3 (13.4)	0.02
DLCO, % predicted	50.4 ± 24.2	63.2 ± 14.5	67.5 ± 16.8	52.8 (17.2)	<0.0001
Radiographic pattern					
Fibrotic	22 (63%)	5 (71%)	14 (82%)	57 (100%)	
Non-fibrotic/inflammatory	3 (8%)	2 (29%)	1 (6%)	0	N/A
Mixed	10 (29%)	0	2 (12%)	0	

Data given as mean ± standard deviation, or n (%)

ANNA PODOLANCZUK, MD / RESEARCH FELLOW, PULMONARY, ALLERGY AND CRITICAL CARE MEDICINE / COLUMBIA UNIVERSITY MEDICAL CENTER / NEW YORK, NEW YORK, UNITED STATES

Quantitative CT Densitometry Detects Subclinical Interstitial Lung Disease and Predicts Mortality in Community Dwelling Adults: The MESA Lung Fibrosis Study

AUTHORS: Anna Podolanczuk, MD; Elizabeth Oelsner, MD; R. Graham Barr, MD, DrPH; John H. M. Austin, MD; Robert C. Basner, MD; Matthew Bartels, MD; Paul Enright, MD; Bernadette R. Gochuico, MD; Karen Hinckley-Stukovsky, MS; Eric Hoffman, PhD; Joel Kaufman, MD, MPH; P. Hrudaya Nath, MD; John Newell, MD; Dan Rabinowitz, PhD; Jered Sieren; Russell Tracy, PhD; Ganesh Raghu, MD; Sushil K. Sonavane, MD; Jubal R. Watts, MD; Kayleen Williams, MPH; Steven Kawut, MD, MS; David J. Lederer, MD, MS

GENERAL AUDIENCE SUMMARY

OBJECTIVES: We sought to investigate the validity of high attenuation areas (HAA) as a quantitative CT-based phenotype of subclinical ILD by examining its association with FVC, serum matrix metalloproteinase-7 (MMP-7), interstitial lung abnormalities (ILA) and mortality.

METHODS: We performed cross-sectional and longitudinal analyses of participants in Multi-Ethnic Study of Atherosclerosis (MESA), which enrolled community-dwelling men and women ages 45–84 without cardiovascular disease in 2000-2002. Participants completed baseline cardiac CT scans, which were analyzed using automated CT densitometry for presence of HAA, defined as the percentage of lung voxels having CT attenuation values between -600 and -250 Hounsfield Units. We used generalized linear and additive models to examine associations of log-transformed percent HAA with the above outcomes, adjusting for demographics, anthropometrics, smoking, percent emphysema on CT, educational attainment, and renal function.

RESULTS: MESA participants had a mean age of 62 years; 47% were male; 38% were white, 28% were African-American, 22% were Hispanic and 12% were Asian; 55% were ever-smokers. Among 3834 participants who completed spirometry, greater volume of HAA was associated with lower FVC at 3.7 years of follow-up (mean adjusted difference in FVC per IQR in HAA -57 mL, 95% CI -33 to -81, p-value <0.001; in percent predicted FVC 1.93 percentage points, 95% CI -1.20 to -2.65, p-value <0.001). Among 908 participants with baseline biomarker measurements, a greater volume of HAA was associated with higher serum MMP-7 levels (Figure 1). Among 2430 participants who completed full lung CT scans at 9.5 years of follow-up, greater volume of HAA was associated with higher prevalence of ILA (Figure 2). Greater volume of HAA was also an independent predictor of all cause-mortality at 12.2 years of follow-up in 6807 participants (HR 1.29 per IQR in HAA, 95% CI 1.18 to 1.42, p-value <0.001).

CONCLUSIONS: Greater percent of HAA at baseline was associated with higher baseline levels of MMP-7 as well as lower FVC, higher prevalence of ILA and higher all-cause mortality after longitudinal follow-up. Thus, measurement of HAA may be a biomarker of subclinical ILD and high volume of HAA is a risk factor for mortality.

Figure 1. Continuous association between baseline HAA and MMP-7, adjusted for age, gender, race, educational attainment, height, BMI, waist circumference, smoking status, cigarette pack-years, glomerular filtration rate (GFR), study site, percent emphysema, mA dose and total volume imaged lung. Mean difference in HAA per IQR in log-transformed MMP-7 5.3%, 95% CI 2.41-8.31, p for association <0.001, p for non-linearity 0.01. Dark dotted line = effect estimate; thin dashed lines = 95% confidence bands.
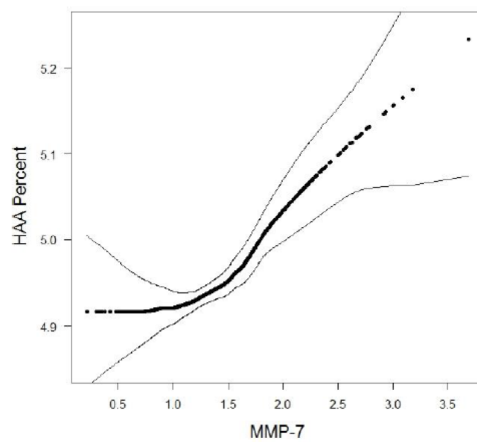
Figure 2. Continuous association between the risk of ILA at 9.5 years of follow-up and baseline HAA, adjusted for age, gender, race, educational attainment, height, BMI, waist circumference, smoking status, cigarette pack-years, glomerular filtration rate (GFR), study site, percent emphysema, mA dose and total volume imaged lung. PR for ILA per IQR in HAA 2.14, 95% CI 1.36 to 3.37, p for association <0.001, p for non-linearity 0.17. Dark dotted line = effect estimate; thin dashed lines = 95% confidence bands.
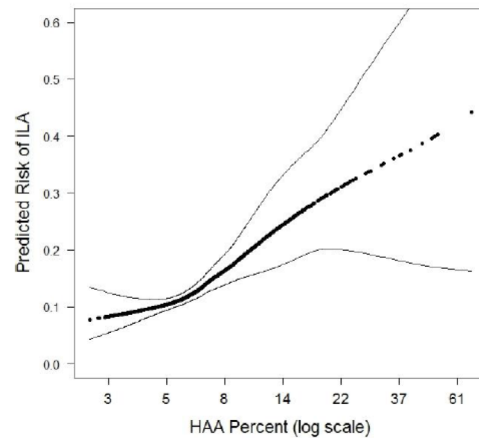
LUCA RICHELDI, MD, PHD / PROFESSOR OF RESPIRATORY MEDICINE, CHAIR OF INTERSTITIAL LUNG DISEASE / NATIONAL INSTITUTE FOR HEALTH RESEARCH / SOUTHAMPTON RESPIRATORY BIOMEDICAL RESEARCH UNIT AND CLINICAL AND EXPERIMENTAL SCIENCES / SOUTHAMPTON, UNITED KINGDOM

Effect of dose reductions, treatment interruptions and dose intensity on decline in lung function with nintedanib in patients with idiopathic pulmonary fibrosis (IPF): results from the INPULSIS® trials

AUTHORS: Luca Richeldi[1], Ulrich Costabel[2], Yoshikazu Inoue[3], Susanne Stowasser[4], Toshio Kimura[4], Arata Azuma[5]

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GENERAL AUDIENCE SUMMARY

OBJECTIVES: The two replicate, randomized, placebo-controlled, 52-week INPULSIS® trials assessed the efficacy and safety of nintedanib 150 mg twice daily (bid) in patients with IPF. Compared with placebo, nintedanib significantly reduced the annual rate of decline in forced vital capacity (FVC) in both trials. Dose reductions from 150 mg bid to 100 mg bid and treatment interruptions were allowed for the management of adverse events. We assessed whether dose reductions and treatment interruptions influenced the effect of nintedanib.

METHODS: We assessed change from baseline in FVC at week 52 in patients treated with nintedanib who did or did not have ≥1 dose reduction, treatment interruption, or dose reduction and/or treatment interruption, and in patients with dose intensity ≤90% versus >90% using pooled data from both INPULSIS® trials.

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117

RESULTS: The number of patients within each subgroup is shown in the Table. Mean dose intensity in the nintedanib group was 93.7%.In patients who did or did not have ≥1 dose reduction, absolute mean changes from baseline in FVC at week 52 were –88.3 mL and –89.1 mL, respectively. In patients who did or did not have ≥1 treatment interruption, absolute mean changes from baseline in FVC at week 52 were –77.3 mL and –92.4 mL, respectively. In patients who did or did not have ≥1 dose reduction and/or treatment interruption, absolute mean changes from baseline in FVC at week 52 were –87.5 mL and –89.6 mL, respectively. Absolute mean changes from baseline in FVC at week 52 were –72.0 mL and –94.2 mL in patients with dose intensity ≤90% and >90%, respectively.

CONCLUSION: Pooled data from the INPULSIS® trials show that the decline in FVC was similar in patients treated with nintedanib irrespective of dose intensity, indicating that the dosing regimen, which allowed for dose reductions and treatment interruptions to manage adverse events, was effective in patients with IPF.

N (%)	Nintedanib (n=638)	Placebo (n=423)
Dose reduction		
Patients who had ≥1 dose reduction	178 (27.9)	16 (3.8)
Patients who did not have ≥1 dose reduction	460 (72.1)	407 (96.2)
Treatment interruption		
Patients who had ≥1 treatment interruption	151 (23.7)	42 (9.9)
Patients who did not have ≥1 treatment interruption	487 (76.3)	381 (90.1)
Dose reduction and/or treatment interruption		
Patients who had ≥1 dose reduction and/or treatment interruption	220 (34.5)	46 (10.9)
Patients who did not have ≥1 dose reduction and/or treatment interruption	418 (65.5)	377 (89.1)
Dose intensity*		
Patients with dose intensity ≤90%	154 (24.1)	18 (4.3)
Patients with dose intensity >90%	484 (75.9)	405 (95.7)
Patients who had ≥1 dose re-escalation to 150 mg bid	40 (6.3)	7 (1.7)
Patients who finished the study on 150 mg bid	487 (76.3)	414 (97.9)

*Amount of drug administered divided by amount that would have been received had the 150 mg bid dose been administered throughout the study or until permanent discontinuation of study medication.

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Addition of rheumatologic evaluation and capillaroscopy as part of the initial ILD encounter

AUTHORS: Ashleigh Rodriguez, MSN; Gordon Carr, MD; Kenneth Knox, MD; Abigale Nastase, RN; Rafael Grau, MD

GENERAL AUDIENCE SUMMARY

OBJECTIVES: In interstitial lung disease (ILD), data suggest a care team model incorporating multidisciplinary decision-making with a radiologist, pathologist and pulmonologist is important and should be a standard approach to these patients. Given that many patients diagnosed with pulmonary fibrosis have a yet to be defined connective tissue disease (CTD), rheumatologic evaluation is often necessary to determine subtleties of CTD and autoimmune diseases. Moreover, as therapies for CTD-ILD and idiopathic pulmonary fibrosis (IPF) are presently different, categorizing patients appropriately has emerging therapeutic implications. Our multidisciplinary clinical approach incorporates rheumatologic evaluation, including capillaroscopy, for all new patients with ILD.

METHODS: The ILD clinic at Banner – University of Arizona Medical Center has over 165 patients in their prospective IRB approved registry with 12% diagnosed with IPF. A rheumatologist with expertise in scleroderma evaluates all patients as part of routine clinical care at the first ILD visit. Examination focuses on skin findings and capillaroscopy. Fourth and fifth digit capillaries were examined under magnification and abnormalities were graded as to density and morphological changes according to established criteria.

RESULTS: 47 patients underwent capillaroscopy with 25 being categorically abnormal and 7 being "indeterminate". Abnormalities were seen in 74% of 27 patient with confirmed or suspected CTD, 25% of 8 patients with probable or confirmed hypersensitivity pneumonitis, 50% of 6 patients with other ILD, and 0% of 6 patients with probable or confirmed IPF. In 26 cases, rheumtologic evaluation with skin findings, auto-antibody interpretation, and capillaroscopy influenced the diagnoses, treatment or course of care.

CONCLUSION: In a multidisciplinary care model, addition of up front rheumatologic evaluation with capillaroscopy was useful in categorizing some cases of ILD and may have an influence on therapeutic decision making in the era of anti-fibrotic therapies.

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.... 119

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Activation of myofibroblast-associated genes by Thymosin beta4 in Idiopathic Pulmonary Fibrosis derived fibroblast cell lines

AUTHORS: L. Rodriguez; R. Novak; S. D. Nathan; G. Grant

GENERAL AUDIENCE SUMMARY

RATIONALE: The idiopathic pulmonary fibrosis (IPF) lung is plagued by an abundance of activated fibroblasts (myofibroblasts). These fibroblasts appear to evade apoptotic cues under conditions of high oxidative stress which is present in the IPF lung. Thymosin-beta4 (Tß4) is a cytoskeleton regulatory protein with diverse capabilities including profibrotic activities and decreasing the oxidative stress response. Tß4 is upregulated in primary fibroblasts isolated from IPF lungs. The objective of this study was to investigate the potential role of Tß4 in regulating myofibroblast activating signals and oxidative stress in IPF fibroblasts.

METHODS: Analysis of gene expression comparing IPF-F (n=4) and N-F (n=4) at passage zero was carried out using the TM4 microarray software suite. Ontological analysis was carried out using the Database for Annotation, Visualization and Integrated Discovery (DAVID). To evaluate the effect of Tß4 on fibroblast activation status, IPF-F and N-F cells were exposed to 0, 5, 10 and 20 µg/ml Tß4 (RegeneRx, MD) over a 24 hour period. Myofibroblast associated marker gene expression alpha smooth muscle actin (ACTA2), N-cadherin (NCAD), vimentin (VIM), and transforming growth factor beta (TGFß) were monitored by Q-PCR.

RESULTS: DAVID ontological analysis of the gene expression data revealed a significant enrichment (enrichment score 5.86 p = 8.09 E-9) of actin cytoskeletal associated processes, extracellular matrix-associated genes (enrichment score 3.0 p = 5.51 E-9), mitochondrial- associated genes (enrichment score 4.29 p = 8.5 E-10), and membrane bound vesicle-associated genes (enrichment score 3.43 p= 2.8 E-5). Exposure to Tß4 resulted in an increased expression of ACTA2 (3.33-3.85 fold (n=4 p<0.01)), NCAD (5.68-7.08 fold (n=4 p<0.01)), VIM (1.68-2.68 fold (n=4 p<0.01), and TGF-ß (1.10-1.51 fold (n=4 p<0.05)) in IPF-F relative to N-F.

CONCLUSION: The up-regulation of Tß4 observed in IPF-F may lead to increased activation of fibroblasts within the IPF lung as demonstrated by the ectopic administration of Tß4 to IPF-F and N-F in vitro. Taken together these data support a novel role for free Tß4 within the complex environment of the diseased fibrotic lung.

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Interplay between aging and lung fibrosis in experimental lung cancer metastases

AUTHORS: Jesse Roman; Aneesha Carter; John C. Greenwell; Edilson Torrez-Gonzalez; Glenn Vicary; Jeffrey D. Ritzenthaler

GENERAL AUDIENCE SUMMARY

OBJECTIVE: Lung cancer is the number one cause of cancer death in the world. Despite new knowledge about the biology of lung cancer, its 5-year survival rate remains at a dismal 15%. Most lung cancers develop in elderly people with chronic lung disease characterized by chronic inflammation and tissue remodeling. Thus, we hypothesize that aging and lung inflammation/remodeling act in concert to promote lung cancer progression.

METHODS: To test the hypothesis, we engaged in studies using young and aging C57BL mice in conjunction with bleomycin treatment and a xenograft model of experimental lung cancer. The flanks of control and bleomycin-treated young (3.7 months of age) and aging (9.5 months of age) mice were injected with Lewis Lung Carcinoma (LLC) cells (1 x 106) at day 14 after bleomycin injection. Afterwards, the animals were euthanized and the lungs underwent bronchoalveolar lavage and processed for histology. We also cultured LLCs with primary lung fibroblast-conditioned media and tested proliferation, migration, and cisplatin-induced apoptosis.

RESULTS: Using the xenograft model, we found that untreated aging mice developed more lung metastases than young mice. We then turned our attention to the effects of bleomycin and found that, as expected, bleomycin induced weight loss and lung inflammation/remodeling in both young and aging mice. In animals injected with LLCs, the size of the subcutaneous tumors were similar at the time of euthanasia ($p = 0.2$). However, bleomycin treatment further enhanced the number of lung metastases in the aging mice ($p=0.0002$). Finally, to learn about the host factors involved, we cultured LLCs in the conditioned media of primary lung fibroblasts. Fibroblast derived media stimulated the proliferation and migration of LLCs, and reduced their susceptibility to cisplatin-induced apoptosis; media from aging fibroblasts was not as protective.

CONCLUSIONS: Our studies suggest that age-dependent host factors influence lung cancer progression, and lung fibroblasts might be responsible for some of these events. Importantly, based on studies in the bleomycin model, we conclude that lung inflammation and tissue remodeling enhance pulmonary metastasis in the aging lung, but not in the young lung, thereby

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··· 121

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Impact, Survival, Symptoms and Management: US & UK Patient Perceptions of Living with Idiopathic Pulmonary Fibrosis

AUTHORS: Russell AM; Scholand MB; Snyder EA; Russell AD; Doyle AM; Burdett C; Lasky JA; Renzoni E; Wells AU; Saketkoo LA

GENERAL AUDIENCE SUMMARY

OBJECTIVES: Clinical trials research has provided much consideration into priority endpoints in IPF. Trial design currently hinges on clinician expertise. This work aims to gain patient perspective into priority aspects of treatment and survival in IPF for consideration in endpoint priorities as well as enhancing management.

METHODS: Four focus groups were conducted on a convenience sample of English-speaking adults diagnosed with IPF at 3 academic referral centers in the US and UK. The research team created a safe environment to enable free flowing discussion. Prompts were as necessary for clarification and expansion of patient-presented concepts. Groups were audio-recorded with recordings transcribed verbatim. Transcripts underwent independent analysis using inductive methodology. Each of the four transcripts was deconstructed to basic concepts by at least four of six independent analysts, including a carer and a clinical psychologist with special interest in IPF. The analysts engaged in an iterative process to identify core themes and sub-themes therein. The iterative process included independent reading and re reading, individual thematic analysis and group discussion

RESULTS: 12 patients in the UK (m=7) and 14 patients in the US (m=10) representing the spectrum of IPF disease severity, according to Composite Physiological Index classification discussed their experiences of living with IPF. A Patient and Public involvement officer attended the UK groups. By this method, a conceptual framework of 9 domains with related concepts were identified (table 1) characterising both intrinsic and extrinsic factors that impact living with IPF. Patients reported that focus group participation was a positive and supportive experience and expressed an interest in meeting again.

CONCLUSION: Bringing together patients from the full spectrum of severe to mild disease has enabled us to characterize the experiential journey of the IPF patient across the disease trajectory in a UK and US population. The conceptual framework identifies core domains and patient generated concepts that can be mapped to World Health Organization International Classification of Functioning, Disability and Health (WHO ICF) to generate endpoints that are clinically meaningful.

Table 1. Domains are in BOLD, domain-associated concepts are in normal type with specifications in *italics*.

SYMPTOM BURDEN	PHYSICAL ENVIRONMENT	DISEASE MANAGEMENT	PSYCHOSOCIAL MANAGEMENT
Cough Breathlessness Reduced Function *- Mobility* *-Other physical activity* Lack of Appetite Fatigue Anxiety *-acute respiratory decline* *-medication efficacy* *-medication side effects*	Steps/Incline Weather Temperature Outdoor air Indoor air Smoke Pollution Steam Odor/scents	Managing oxygen *-Related danger* *-Physical aspects* *-Enhance Function* Pulse oximetry: *-Pacing* Listening to body *-Pacing* *-Symptoms management* Medication: *-Decisions* *-Minimizing Side Effects* Pulmonary Rehabilitation: *-Enhance function* *-Learning to Breath* *-Learning cough control*	Shared experiences with other patients Positive outlook rooted in realism Impact of pulmonary function testing Setting short-term goals Setting medium-term goals Maintaining Autonomy
	UNCERTAINTY	LIFE CHANGES	ADVANCED PREPAREDNESS
	Disease knowledge Access to therapy Impact of therapy Disease trajectory Reliability of PFTs	Quitting work Progressive disability Probable mortality Roles of Self Roles of Family	Household changes to accommodate disability Financing: wages, housing, setting up disability insurance/welfare Forethought for Daily tasks and activities
		COMMUNICATION	KNOWLEDGE
		Health care providers Loved ones	Lack of reliable published communication Access to knowledge Health care provider knowledge

RUTH SABELLA, BSC / PROJECT MANAGER / BRITISH LUNG FOUNDATION / LONDON, UNITED KINGDOM

Obtaining information when you have a rare disease—the potential for IPF support groups

AUTHORS: R Sabella; S Wibberley; Y Ochiai; R Pitt; N Mathieson

GENERAL AUDIENCE SUMMARY

OBJECTIVES: Our aim was to explore the ways in which patients with IPF obtain information about their condition.

METHODS: Market research was conducted with an independent agency. Patients were asked to record a personal account of their IPF experience on a hand-held camera. Face to face interviews with patients were conducted in their home. Where possible, their main carer was also interviewed, adding an alternative perspective to the findings.

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PFF
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FROM BENCH
TO BEDSIDE

.... 123

RESULTS: The sample included 13 male and 3 female patients. A wide spectrum of IPF severity was included, from mild to severe, five patients were treated with oxygen therapy and another had received a lung transplant. Patients reported finding information from a variety of sources, including primary healthcare professionals, patient information leaflets, the internet, district nurses and support groups. Most valued sources of information were IPF physicians, nurse specialists and patient support groups. Gaps identified by patients where there was a need for high quality information included, 1) accurate and honest information about IPF, 2) clarity on the difficulty of predicting life expectancy, 3) how to access services and benefits, 4) how palliative care can help, 5) why support groups are beneficial, 6) how to modify lifestyle as capabilities change, 7) how to live and travel with oxygen and 8) how to explain oxygen to others.

CONCLUSIONS: Support groups are under-developed, with great potential to help patients and their carers. Support groups are well placed to provide advice for everyday living that the healthcare community may be unable to offer. There is also a need to improve the standard of written information currently available for patients with IPF.

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The emotional turmoil of IPF

AUTHORS: R Sabella; S Wibberley; Y Ochiai; R Pitt; N Mathieson

GENERAL AUDIENCE SUMMARY

OBJECTIVES: Our aim was to understand the emotions patients experience in IPF, from initial symptoms to IPF specialist management.

METHODS: Market research was conducted with an independent agency. Patients were asked to record a personal account of their IPF experience on a hand-held camera. Face to face interviews with patients were conducted in their home. Where possible, their main carer was also interviewed, adding an alternative perspective to the findings.

RESULTS: The sample included 13 male and 3 female patients. A wide spectrum of IPF severity was included, from mild to severe, five patients were treated with oxygen therapy and another had received a lung transplant. There was a national spread geographically throughout England.

Many patients had a very active lifestyle before developing IPF, leading to a high degree of frustration with the limitations imposed on their physical ability. A protracted time to diagnosis of a rare lung disease while symptoms progressed often led to distrust with their primary healthcare physician. Lack of expert knowledge about the condition often resulted in variable handling of the situation, with patients often finding themselves informing their primary healthcare physician about their own condition.

IPF specialists were perceived as their "guardian angels". Despite being given a terminal diagnosis, patients felt reassured that they were receiving appropriate management for their condition. This stemmed from the perception that specialists treating them had appropriate knowledge and a feeling that the patients were supported by the specialist team.

CONCLUSIONS: As with other rare diseases, patients appear to gain most reassurance from HCP's with a clear understanding of their condition. This highlights the benefit of expert multidisciplinary teams for IPF.

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The IPF Diagnosis—Communicating a Life Sentence

AUTHORS: R Sabella; S Wibberley; Y Ochiai; R Pitt; N Mathieson

GENERAL AUDIENCE SUMMARY

OBJECTIVES: Our aim was to explore the patients' emotional experience of receiving a diagnosis of IPF.

METHODS: Market research was conducted with an independent agency. Patients were asked to record a personal account of their IPF experience on a hand-held camera. Face to face interviews with patients were conducted in their home. Where possible, their main carer was also interviewed, adding an alternative perspective to the findings.

RESULTS: The sample included 13 male and 3 female patients. A wide spectrum of IPF severity was included, from mild to severe, five patients were treated with oxygen therapy and another had received a lung transplant. There was a national spread geographically throughout England.

There is a fine balance to providing information and patients can benefit from an individually tailored approach. Too much information at the start can be overwhelming. Too little information can leave the individual uncertain about how to deal with their future. Gaps that were identified focused on the practicalities of living with IPF, including social care. There was a high expectation for their physician to explain why they have developed IPF. Patients felt a blame culture exists, whereby others felt that IPF is self-inflicted, like COPD, particularly when a patient was taking oxygen therapy. Patients may be left with feelings of anger at missed opportunities and concern for lost years of intervention and appropriate palliative care support.

CONCLUSIONS: The diagnosis of IPF is a devastating one, which can be challenging to manage. Carers, patient groups and expert support at diagnosis were found to be invaluable to patients during this time.

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.... 125

LESLEY ANN SAKETKOO, MD / DIRECTOR, NEW ORLEANS SCLERODERMA AND SARCOIDOSIS PATIENT CARE
AND RESEARCH CENTER / TULANE UNIVERSITY SCHOOL OF MEDICINE / NEW ORLEANS, LOUISIANA, UNITED STATES

Mycophenolate Use (MMF) in Systemic Sclerosis (SSc) Patients with a Designation of Elevated Systolic Pulmonary Artery Pressure (sPAP): Forced Vital Capacity (FVC), Outcomes and Survival from the European Scleroderma Trials and Research (EUSTAR) Database

PRESENTER: Joseph A. Lasky, MD

AUTHORS: Saketkoo LA; Huscher D; Denton CP; Riemekasten G; Steen VD; Distler O; Lasky J

RESEARCH SUPPORT: Lerner Research Institute, Department of Pathobiology, Cleveland Clinic

GENERAL AUDIENCE SUMMARY

OBJECTIVE: SSc-related PH carries a high mortality; with SSc-PH related to restrictive lung disease (RLD) having worse prognosis and more rapid time to death. Speculation regarding potential MMF anti-fibrotic and anti-remodeling effects on lung parenchymal and vascular intimal fibrosis were supported by two prior large US and UK observational studies. Here, we analyzed predictive markers of mortality of PH stratified for RLD and for MMF use in the prospective EUSTAR database of >12,000 SSc patients.

METHODS: SSc patients with a registry designation of elevated sPAP by either RHC or, in absence of RHC, by echocardiography were stratified by FVC of >70% or <70% predicted near time of PH-designation and by MMF use. MMF <6 months or cyclophosphamide use were excluded. Calculations are derived from one-way ANOVA. Categorical variables and survival were compared with Chi-square and Kaplan-Meier analysis respectively.

RESULTS: Of 11,721 patients fulfilling ACR-EULAR criteria, 1,264 matched criteria and had baseline PFTs coincident with PH designation, of those 965 had a baseline FVC of >70% with 43 on MMF and 927 without; and 294 had a baseline FVC<70% with 22 on MMF and 272 without. Diagnosis by RHC occurred in 263/1264 patients; the remaining were designations by echocardiogram. There were no differences in disease duration. The FVC<70 MMF+ group was significantly younger with worse NYHA status and disease activity. In both FVC<70 (RLD) groups, FVC, DLCO and FVC:DLCO ratio were significantly lower while presence of fibrosis on HRCT and diffuse SSc-subtype significantly higher. Survival assessed numerically and by Kaplan-Meier were significantly the worst with FVC<70 without MMF and best with FVC<70 with MMF across 2 (p=0.001) and 3, 4, 5 years (p<0.0001) despite significantly worse disease activity score and NYHA class over the 4 groups.

CONCLUSION: Registry data trends suggest an association of MMF with beneficial survival in SSc-PH. Study limitations include mixed diagnostic methods of PH and inclusion of non-RHC diagnoses. These findings warrant further analysis of international PH-SSc cohorts to determine whether a prospective controlled trial may be developed to test mechanisms and impact of MMF in treating this important complication of SSc.

Table 1. Comparison between the baseline characteristics of the four groups at time of PH diagnosis, Values reported in mean, unless otherwise stated.

	FVC >70% +MMF	FVC >70% - MMF	FVC <=70% +MMF	FVC <=70% - MMF	
Number (1264 total)	43	927	22	272	
Age – yrs, mean	59±11.6	63.4±12	47.9±11.2	58.3±13	p<0.001
Disease Duration yrs, mean	8.9±10.4	11.5±9.2	9.2±7.7	10.2±8.6	p=0.075
Female sex%(n)	65.1 (28)	86 (803)	63.6 (14)	80.1 (218)	p<0.001
EScSG Disease Activity Index >=3	20.9%(9)	23.9%(222)	50.0% (11)	38.6%(105)	p<0.001
Diffuse cutaneous %(n)	48.8 (21)	21.6 (198)	68.2 (15)	53% (142)	P<0.001
Skin score, mean	9.1+6.9	7.7+6.8	12.8±8.4	10.8±9.1	p<0.001
Scl-70 Antibody	40(16)	24.3(198)	66.7(14)	56.8(134)	
Presence of Fibrosis on HRCT %(n)	63.6 (21)	44.2 (258)	85.7 (18)	77.5 (162)	p<0.001
NYHA Class III/IV %(n)	27.5(11)	23.1(199)	66.7 (14)	49.8 (123)	p<0.001
FVC% predicted	89.2±15	97.8±17.6	56.0±9.4	56.5±10,4	p< 0.001
DLCO % predicted	50.8±17.1	62.1±20.2	40.9±13	43±17	p<0.001
FVC:DLCO Ratio	2.0±0.7	1.7±0.6	1.5±0.5	1.5±0.5	p<0.001
RHC performed %(n)	25.6 (11)	21.2 (196)	40.9 (9)	24.6 (67)	

Diagram 1. Survival across all groups stratified by FVC and MMF use.
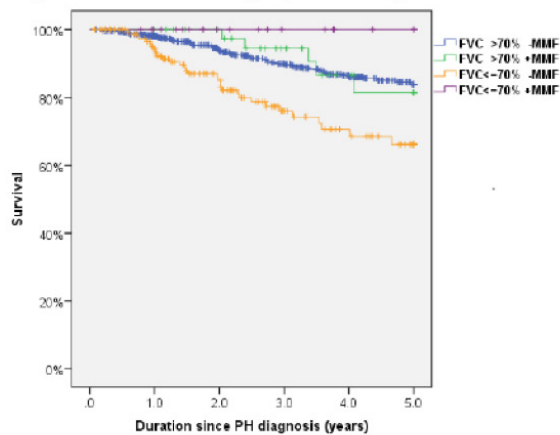
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Radiographic and Clinical Predictors of Idiopathic Pulmonary Fibrosis in Absence of Honeycombing

AUTHORS: Margaret Salisbury; Meng Xia; Susan Murray; Brian J. Bartholmai; Catherine Meldrum; Fernando J. Martinez; Kevin. R. Flaherty

GENERAL AUDIENCE SUMMARY

OBJECTIVES: Idiopathic pulmonary fibrosis (IPF) can be diagnosed confidently and non-invasively when clinical and high-resolution computed tomography (HRCT) criteria are met. Many individuals do not meet these criteria due to the absence of radiographic honeycombing. We investigated predictors of IPF and combinations allowing accurate diagnosis of IPF in individuals without honeycombing.

METHODS: We conducted a retrospective analysis of prospectively collected clinical and radiographic data from patients enrolled from five tertiary referral centers into the Lung Tissue Research Consortium (LTRC). Included were patients with interstitial lung disease (ILD) diagnosis confirmed by clinical, radiographic, and pathologic criteria, without evidence of connective tissue disease, and having IPF, nonspecific interstitial pneumonia, or chronic hypersensitivity pneumonia HRCT patterns without radiographic honeycombing (n=227). Logistic regression identified clinical and radiographic variables predictive of IPF. These variables were combined and specificity, positive predictive value, sensitivity and negative predictive value for IPF calculated.

RESULTS: Our cohort included 52.9% males with mean age 63.5 years, percent-predicted forced vital capacity 62.7%, and IPF prevalence 70.5%. Multivariate analysis found higher age (OR 1.22, CI 95% 1.01-1.48, p=0.043), male gender (OR 1.96, CI 95% 1.01-3.77, p=0.045), and increasingly extensive HRCT reticular densities (OR 2.17, CI 95% 1.21-3.88, p=0.010) predicted IPF; increasing ground glass densities predicted a diagnosis other than IPF (OR 0.56, CI 95% 0.38-0.84, p=0.005). For ages = 65 years with reticular density whole lung composite = 1.5, the specificity for IPF was 99% with 95% positive predictive value.

CONCLUSIONS: In patients with suspected ILD and absence of radiographic honeycombing, higher age and extensive reticular densities suggest a diagnosis of IPF. In combination, modest age and extent of reticular densities provide high specificity and positive predictive value for IPF.

RACHEL SCHERAGA, MD / ASSOCIATE STAFF, RESPIRATORY INSTITUTE, LERNER RESEARCH INSTITUTE / CLEVELAND CLINIC FOUNDATION / CLEVELAND, OHIO, UNITED STATES

The mechanosensitive transient receptor potential vanilloid 4 (TRPV4) ion channel mediates the pro-resolution/anti-fibrotic macrophage response to endotoxin (LPS)

AUTHORS: Rachel Scheraga; Susamma Abraham; Kathryn A. Niese; Brian D. Southern; Lisa M. Grove; Thomas Hamilton; Mitchell A. Olman

GENERAL AUDIENCE SUMMARY

OBJECTIVES: Macrophage phagocytosis is essential to innate immunity and the lung injury/repair response. Phagocytosis depends on the orchestration of macrophage surface receptors, the particle itself, and the extracellular matrix (1-5). TRPV4 is a stretch-sensitive cation channel implicated in lung diseases associated with lung parenchymal stretch (6-11). We undertook this study to test the hypothesis that TRPV4 integrates the extracellular matrix stiffness and LPS signals, thereby mediating the key elements of the host defense and lung injury/repair response to bacterial pneumonia.

METHODS: Bone marrow-derived macrophages (BMDMs) and alveolar macrophages from C57BL/6 mice were plated on fibronectin-coated polyacrylamide hydrogels of varying stiffness (1, 8, 25 kPa) or glass (1X106 kPa). The macrophages were incubated ± LPS (E. coli 0111:B4; 100 ng/ml, 6-24 hrs), ± TRPV4 inhibitor (HC) ± TRPV4 siRNA or controls, and ± TRPV4 KO BMDMs. Cytokines were measured in conditioned media by ELISA. Phagocytosis was measured by uptake of fluorescently-labeled E. coli particles or IgG-coated latex beads. The intracellular calcium rise in response to a TRPV4 agonist (GSK) was evaluated using a calcium sensitive dye.

RESULTS: LPS increased macrophage phagocytosis of E. coli particles and IgG-coated latex beads in murine WT BMDMs. This effect was abrogated upon TRPV4 pharmacologic inhibition (HC), its downregulation (siRNA), and its deletion (KO). A similar blockade of LPS-induced phagocytosis was seen in alveolar macrophages upon TRPV4 deletion in vitro, and in the lungs of live TRPV4 KO mice. LPS induction of macrophage phagocytosis depends on extracellular matrix stiffness, in a range seen in injured/fibrotic lung (25 kPa). TRPV4 mediates a pro-resolution/anti-fibrotic cytokine profile in response to LPS (?IL-10 and ?IL-1ß) in a manner that similarly depends on matrix stiffness.

CONCLUSIONS: These findings suggest that TRPV4 integrates the LPS and extracellular matrix signals for phagocytosis and increases pro-resolution/anti-fibrotic cytokine production to promote lung injury resolution. These mechanisms are likely to be important in regulating macrophage function in the context of pulmonary infection and fibrosis.

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Mechanical stress and mast cell activation in TGFß-1 induced rat pulmonary fibrosis

AUTHORS: Chiko Shimbori; Pierre-Simon Bellaye; Jack Gauldie; Martin Kolb

GENERAL AUDIENCE SUMMARY

OBJECTIVES: Many mast cells are found in fibrotic areas in IPF lungs, but very little is known about their role in fibrosis. Our preliminary work in rat demonstrated that mast cells are increased in fibrotic lesions only in the chronic phase of progressive pulmonary fibrosis. Our hypothesis is that mechanical stress of fibrotic lung may affect mast cells and thereby contribute to a profibrotic vicious cycle.

METHODS: To study the effects of mast cells on mechanical stretch induced TGF-ß1 activation, we used our unique ex vivo bath model. Pulmonary fibrosis was induced by overexpression of active TGF-ß1 in rats. Fibrotic lung was pre-incubated with 2 different mast cell stabilizers: disodium cromoglycate and doxantrazole for 2 hours prior to submitting the tissue to stretch force. Histamine levels in the bath solution were measured by ELISA. pSmad2/3 and Smad2/3 were detected by Western Blotting in lung strip homogenates. Active TGFß level was measured using the PAI1 luciferase cell assay using bath solution. In an in vivo study, cromolyn sodium (40 mg/ kg/ day, i.p.) was administered from day 14 to day 21 to rats. We analyzed the effect of cromolyn sodium using immunohistochemistry, ELISA, Western Blotting and PCR in lung tissue.

RESULTS: Mechanical stress induced active TGF-ß1 and histamine release into the bath solution and induced pSmad2/3 expression in fibrotic lung tissues. Mast cell stabilizers significantly inhibited histamine release into the bath solution and reduced pSmad2/3 in lung tissue. Cromolyn sodium also tended to decrease active TGF-ß1 content in the bath solution. In the animal study, cromolyn sodium treatment decreased mast cell numbers in lung parenchyma compared with control group. Cromolyn treatment did not change Ashcroft score and soluble collagen content of the lungs. However, it did attenuate fibrotic areas in lung tissue and tended to decrease insoluble collagen content in the lung.

CONCLUSIONS: Our data indicate that mechanical stress can induce mast cell degranulation and contribute to activate TGF-ß1 signaling pathway. Mast cell stabilizers attenuated the mechanical stress induced mast cell degranulation and TGF-ß1 signaling pathway activation, and also show promising effect in TGF-ß1 induced pulmonary fibrosis.

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Comparison of the GAP Model, Composite Physiologic Index and the Lung Allocation Score in Patients with Idiopathic Pulmonary Fibrosis/Interstitial Lung Disease Undergoing Lung Transplantation

AUTHORS: Leann Lashea Silhan; Cheilonda Johnson; Pali D. Shah; Sonye K. Danoff

GENERAL AUDIENCE SUMMARY

BACKGROUND: Idiopathic pulmonary fibrosis (IPF) and other advanced interstitial lung diseases (ILD) are often fatal without lung transplantation (LT). The GAP (gender, age, physiology) model and Composite Physiologic Index (CPI) predict mortality in patients with IPF and ILD but their utility following LT is unknown. The Lung Allocation Score (LAS) is designed to provide priority to those with greatest need for transplant. We compared the predictive power of the LAS, GAP, and CPI model using overall mortality within the first year posttransplant.
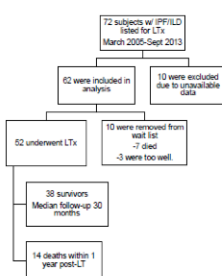
OBJECTIVE: To compare the GAP index, CPI, and LAS scores and evaluate their utility in predicting outcomes within one year post- lung transplant.

METHODS: Retrospective analysis of 72 consecutive patients with IPF or ILD who were listed for lung transplant March 2005 and September 2013 at JHU. Logistic regression models were used to compare the relative contribution and explanatory power of the LAS, GAP, and CPI for predicting mortality within the year posttransplant using likelihood ratio chi-square tests (G2) and the area under the receiver operator characteristic (ROC) curve.

RESULTS: Fifty-two IPF or ILD subjects with complete data received a LT 14 (27%) died within the first year of transplant. All of the prediction indices were poorly correlated (LAS and GAP score; r2=0.033, LAS and CPI; r2=0.036,and GAP score and CPI; r2= 0.184). Of all the prediction scores, only CPI significantly improved the base model (G2=19.6, P=<0.001). Base model included gender, age and race. The predictive power of all three indices was poor (C-statistic range 0.62-0.67).

CONCLUSIONS: Our data suggest that the LAS, GAP score, and CPI perform poorly as predictive models for early post lung transplantation mortality in patients with IPF/ILD. Prediction models for posttransplant outcomes for IPF/ILD are important given limitations in posttransplant outcomes.

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.... 133

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A quality improvement project to improve the screening and treatment of gastroesophageal reflux in patients with idiopathic pulmonary fibrosis

AUTHORS: Joseph H. Skalski MD; Michael E. Wilson MD; Lynn A. Fussner MD; Hemang Yadav MBBS; Ana C. Zamora MD; Praveen Jinnur MBBS; Andrew H. Limper MD

GENERAL AUDIENCE SUMMARY

OBJECTIVES: Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive lung disease with high mortality and few effective therapies. Gastroesophageal reflux (GER) is common in patients with IPF, with prevalence as high as 90%. (Ref 1,2) The impact of GER on patient-important outcomes in IPF remains incompletely characterized, with observational studies suggesting treating GER may be associated with reduced mortality in patients with IPF. (Ref 3,4) Our quality improvement (QI) project aimed to increase the rate of high quality screening for GER symptoms and to increase the rate of appropriate treatment of GER symptoms in new IPF consultations.

METHODS: The DMAIC methodology was used for this QI project. Pre-intervention magnitude measurement was performed by retrospective chart review of all new IPF consultations over a 9-month period. The project team then solicited input from multiple stakeholders including physicians, nursing, and clinical assistants. Multiple QI tools were used to analyze the problem including Pareto chart, Ishikawa diagram, and effort-yield analysis. Ultimately, the primary intervention selected was a survey distributed to each patient at time of rooming that prompted patients to discuss GER symptoms with their physician (Figure 1). After three cycles of revision, the survey was introduced to the clinic rooming process. Three months after survey implementation, a post-intervention chart review was repeated to reassess GER screening and treatment rates.

RESULTS: The pre-intervention chart review screened 478 encounters to identify 45 new IPF patient visits, and the post-intervention chart review screened 133 encounters to identify 10 new IPF patient visits. After the intervention, the rate of optimal screening of GER symptoms improved from 36% to 90% (p=0.001), the rate of optimal medical management of GER improved from 67% to 90% (p=0.35) and the rate of GER symptom control improved from 57% to 80% (p=0.14).

CONCLUSIONS: A patient questionnaire distributed at the time of rooming may increase the rate of high quality screening, treatment, and symptom control for GER in IPF patients.

Heartburn & Reflux Questionnaire

Within the last 6 months:	Yes	No	If yes, how often?
1. Have you had a burning feeling behind your breastbone (heartburn)?	□	□	□ Once a day or more □ A few times a week □ A few times a month □ Rarely
2. Have you had stomach contents (liquid or food) moving upwards to your throat or mouth (regurgitation, acid/burning taste)?	□	□	□ Once a day or more □ A few times a week □ A few times a month □ Rarely
3. Have you had difficulty going to sleep or been awakened at night due to heartburn and/or regurgitation?	□	□	□ Once a day or more □ A few times a week □ A few times a month □ Rarely
4. Do you use medications to treat heartburn (examples: Tums, Rolaids, Maalox, Prilosec, Nexium, etc.)	□	□	□ Once a day or more □ A few times a week □ A few times a month □ Rarely

Please hand this completed form to your doctor when they enter the room.

****Recent studies have shown that treating gastroesophageal reflux (heartburn) in patients with some types of pulmonary fibrosis is beneficial and may help patients live longer.****
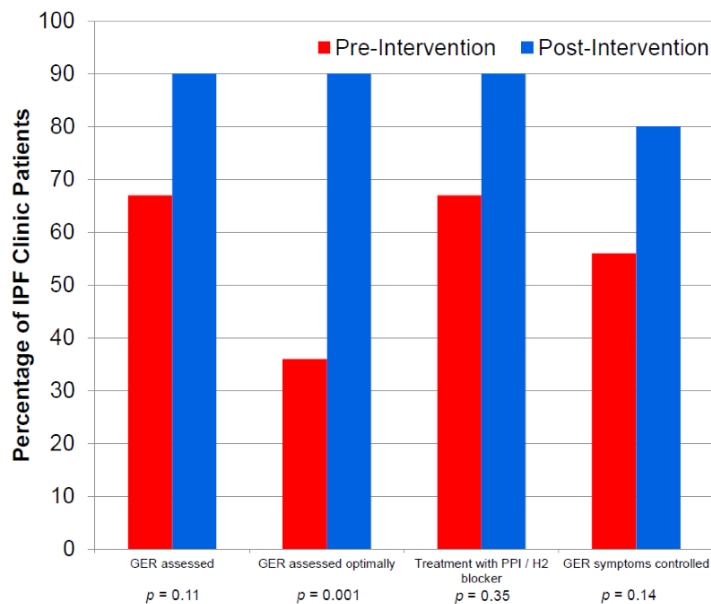
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Idiopathic Pulmonary Fibrosis Fibroblasts Exhibit Matrix-Autonomous Upregulation in Non-Muscle Myosin II

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Dustin Thomas; Thomas T. Egelhoff; Mitchell A. Olman

GENERAL AUDIENCE SUMMARY

OBJECTIVES: Activated fibroblasts play a critical role in the pathogenesis of idiopathic pulmonary fibrosis (IPF) by migrating into areas of ongoing fibrosis and by differentiating into myofibroblasts. However, the signals and effector molecules driving this aberrant accumulation of fibroblasts have not been fully elucidated. Using a system that examines fibroblast-matrix interactions in normal and fibrotic lung, we have already characterized the role of non-muscle myosin II (NMM2) in promoting the pro-fibrotic phenotype in normal human lung fibroblasts (N HLFs). The purpose of this study was to examine the role of matrix-derived NMM2 signaling in IPF patient-derived fibroblasts (IPF HLFs) compared to normal HLFs.

METHODS: Differentially-labeled N HLFs or IPF HLFs were allowed to attach to unfixed murine normal and fibrotic lung tissue (10 μm sections, 45 min) followed by time-lapse videomicroscopy (6 hrs, tracking analysis by ImagePro). Traction force microscopy was performed on 25 kPa fibronectin-coated polyacrylamide gels. NMM2 activity was blocked using blebbistatin and/or siRNA. Myofibroblasts were identified by quantification of F-actin, alpha-smooth muscle actin, and activated myosin (pMLC, 24 hr) by immunofluorescence and/or immunoblotting.

RESULTS: Compared to N HLFs, IPF HLFs have upregulated pMLC (by 42%, p=0.01) and exert greater traction force in response to TGF-beta (43%; p=0.014). In response to either normal or fibrotic lung tissue matrix, IPF HLFs exhibit less polarized migration (57% slower than N HLFs, p<0.001) and more robust myofibroblastic characteristics (66% more alpha-SMA than N HLFs, p<0.001). In contrast, NHLF's have a phenotype (migration and myofibroblast differentiation pattern) that is highly dependent on the type of lung matrix. The response of normal HLF's to lung matrix type is dependent on NMM2 activity.

CONCLUSIONS: These findings suggest that IPF HLFs exhibit a matrix signal-autonomous increase in NMM2 activity that drives a feed-forward up-regulation of the pro-fibrotic phenotype. This dysregulation of the NMM2 activation pathway likely promotes the progression of fibrosis seen in IPF.

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.... 137

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SH2 domain-containing Phosphatase-(SHP)-2 is a novel anti-fibrotic agent in Idiopathic Pulmonary Fibrosis

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Naftali Kaminski

GENERAL AUDIENCE SUMMARY

BACKGROUND: The recent evidence that tyrosine-kinase inhibition may slow down disease progression in patients with idiopathic pulmonary fibrosis (IPF) reignites the interest in regulating signal transduction pathways in lung fibrosis.

OBJECTIVE: To determine the role of SHP2 in lung fibrosis

METHODS AND RESULTS: Reanalyzing a large microarray dataset obtained from lungs of patients with IPF (n=123) and controls (n=96) we discovered that the tyrosine-protein phosphatase non-receptor type 11 (PTPN11), the gene encoding for the SHP2 was downregulated in IPF lungs. qRT-PCR and western blot analyses further confirmed the microarray results on an mRNA and protein level (3- fold decrease). Immunolocalization studies revealed that SHP2 was mostly absent from active fibroblastic foci and co-localized with SP-B positive cells in the normal alveolar epithelium. SHP2 inhibition through siRNA or PHPS1, a pharmacologic inhibitor, promoted fibroblast to myofibroblast differentiation in normal human lung fibroblasts (NHLF) as assessed by increased formation of stress fibers and increase of mRNA and protein expression of a-SMA (4- and 3-fold) and col1a1 (5- and 1.5-fold). SHP2 overexpression reduced the responsiveness of fibroblasts to pro-fibrotic stimuli (10ng/ml TGF-b1) leading to significant reductions in: 1) cell survival, as assessed by increased expression of apoptotic markers (activated caspase-3 and TUNEL) 2) proliferation (3-fold), 3) extracellular matrix secretion (1.5-fold decrease in mRNA and protein expression of col1a1), and 4) myofibroblast differentiation, (2-fold decrease in a-SMA mRNA and protein expression). We identified that SHP2 anti-fibrotic effects were mediated through dephosphorylation of tyrosine-kinase (c-abl) and serine/threonine-kinase (smad3) signaling pathways in NHLF. Nintedanib, a tyrosine-kinase inhibitor, induced SHP2 expression in NHLF. Shp2 inhibition through intraperitoneal administration of PHPS1 enhanced fibrotic response to bleomycin. Restoring Shp2 levels through lentiviral delivery blunted induction of fibrosis following bleomycin.

CONCLUSION: Our data indicate that SHP2 down-regulation predisposes cell lines and animal models to enhanced fibrotic responses identifying SHP2 activation as a novel therapeutic strategy for IPF.

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Patient and Partner "Empowerment" Program in Idiopathic Pulmonary Fibrosis (PPEPP): Improving quality of life in patients and their partners

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GENERAL AUDIENCE SUMMARY

OBJECTIVE: IPF is a progressive, deadly disease with devastating impact on patients' and partner's lives. The prognosis of IPF is comparable to many oncological diseases. While structured patient and partners support programs are widely available in oncology, research on similar programs for IPF is scarce. We evaluated the effect of a short multi-disciplinary program for patients with IPF and their partners on quality of life (QoL).

METHODS: During three afternoons IPF patients and their partners met for PPEPP. The program focused on coping with IPF and was led by a psychologist experienced in group therapy. A pulmonologist, IPF nurse, oxygen supplier, social worker and physiotherapists also gave information. Before and after PPEPP, patients and partners completed the Hospital Anxiety and Depression Scale (HADS), Perceived Stress Scale and an IPF quiz. Patients also filled in the King's Brief Interstitial Lung Disease health status questionnaire (KBILD) and Euroqol5D5L (EQ5D5L), partners the Carer Quality of Life instrument. Wilcoxon signed ranks test was used for analysis. All patients and partners gave written informed consent. Ethical Committee approval was granted.

RESULTS: Fourteen couples participated, divided over two PPEPP groups. Eleven (79%) patients and three (21%) partners were men; median age was 64 (47-74). Patients had a median % predicted FVC of 79 (48-100) and TLCOc of 45 (24-61). In patients and partners HADS improved after PPEPP (12 to 10, $p=0.045$). In patients also the KBILD psychological domain improved (48 to 54, $p=0.025$). The other questionnaires did not show a significant change, the EQ5D5L and IPF quiz trended towards improvement. Patients and partners satisfaction with the PPEPP was high.

CONCLUSION: PPEPP, a short multi-disciplinary empowerment program improves quality of life in patients with IPF and their partners. Patients and partners are followed up to evaluate the long-term effect. More groups will start.

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Implementation of an e-health self-management tool for Idiopathic Pulmonary Fibrosis: a pilot study

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GENERAL AUDIENCE SUMMARY

OBJECTIVE: E-health tools could improve understanding of disease, promote patient participation in care, and capture longitudinal data for clinical and research purposes. This can lead to better and personalised care. We evaluated the feasibility of a web-based patient self-management tool called IPF online and assessed patient satisfaction with the tool.

METHODS: IPF online (www.ipfonline.nl) provides a secured personal platform with information about Idiopathic Pulmonary Fibrosis (IPF), lung function test results, symptom scores, quality of life questionnaires and an e-consult possibility. The tool is designed in a way that patients remain owner of their data, but give digital informed consent for specified clinical or research use. Patients were asked to complete health status questionnaires and report symptoms and medication at baseline and at 14 days. Lung function data were imported. An evaluation form was sent afterwards. The tool remained at their disposal if they wished to continue. Ethical Committee approval was granted.

RESULTS: Fifteen patients were asked to participate, 14 consented and filled in the tool at baseline, 13 at 14 days. The info platform was used 109 times, in 86% the requested info was found. Six patients used the e-consult, in total 18 times. The majority found IPF online easy to use (71%), useful (86%), would recommend it to others (86%) and wished to continue (93%). Eight patients spontaneously continued use after the pilot. Patients suggested adding blood results and more information on medication.

CONCLUSION: IPF online is a feasible web-based patient self-management tool with high user satisfaction. IPF online could facilitate a more active role of patients in care and research.

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MnTBAP Inhibits Bleomycin-Induced Pulmonary Fibrosis by Regulating Canonical Wnt Pathway

AUTHORS: Rajkumar Venkatadri; Clayton Wright; Vivek Kaushik; Juan Sebastian Yakisich; Yogesh Kulkarni; Anand Krishnan V. Iyer; Neelam Azad

GENERAL AUDIENCE SUMMARY

OBJECTIVE: Increased oxidative stress is known to be associated with lung injury and pulmonary fibrosis. We observe that superoxide plays a critical role in bleomycin-induced pulmonary fibrosis and Mn(III)tetrakis(4-benzoic acid) porphyrin (MnTBAP), a superoxide dismutase (SOD) mimetic has an inhibitory effect. The objective of the study is to elucidate the effect of MnTBAP on bleomycin-induced pulmonary fibrosis and investigate the underlying mechanisms.

METHODS: Cell proliferation was analyzed by spectrophotometry by assessing incorporation of CyQUANT® (Invitrogen) DNA binding fluorescent dye. Hematoxylin and eosin staining of lung tissue sections was performed to analyze fibrosis in vivo. Soluble collagen levels were quantified by Sircol® Assay (Biocolor Ltd, Belfast, UK) as per manufacturer's protocol. Reactive oxygen species (ROS) levels were measured by spectrofluorometry using specific fluorescent dyes. ROS levels in lung and liver homogenates were measured by TBARS assay. Protein expression was analyzed by Western blotting and soluble protein levels were quantified using ELISA.

RESULTS: MnTBAP significantly inhibited bleomycin-induced collagen levels and lung fibroblast proliferation. Lung histology data showed decreased interstitial fibrosis of the alveolar wall in mice pre-treated with MnTBAP as compared to bleomycin treated mice. MnTBAP significantly inhibited bleomycin-induced cellular superoxide levels and ROS levels in lung tissues and liver homogenates. MnTBAP exerted its inhibitory effect via downregulation of key proteins of the canonical Wnt signaling including pLRP6, LRP6, Wnt 5a/b, Dvl2 and ß-catenin all of which were upregulated in response to bleomycin exposure. Furthermore, MnTBAP significantly inhibited bleomycin-induced VEGF and IL-8 levels in both in vitro and in vivo samples. Interestingly, VEGF and IL-8 proteins were observed to be upstream of Wnt signaling.

CONCLUSION: MnTBAP exerts its effect on bleomycin-induced pulmonary fibrosis by downregulating canonical Wnt signaling via regulation of VEGF and IL-8. Overall, our data reveals novel inhibitory effects of MnTBAP in bleomycin-induced pulmonary fibrosis.

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.... 141

CHRISTINE VIGELAND, MD / FELLOW, PULMONARY AND CRITICAL CARE / JOHNS HOPKINS UNIVERSITY – SCHOOL OF MEDICINE / BALTIMORE, MARYLAND, UNITED STATES

mTORC-Dependent T Cell Differentiation Regulates the Development of Pulmonary Fibrosis

AUTHORS: CL Vigeland; Y Chan Li; MH Oh; SL Collins; JD Powell; MR Horton

GENERAL AUDIENCE SUMMARY

OBJECTIVES: Pulmonary fibrosis is a rapidly progressive lung disease characterized by chronic inflammation and immune activation, which leads to increased deposition of extracellular matrix proteins and fibroblasts. The role of T cells in this disease is poorly understood. Mechanistic target of rapamycin complex (mTORC) is a signaling complex that regulates T cell differentiation. T cells lacking mTORC1 signaling are unable to differentiate into Th1 and Th17 cells, while those lacking mTORC2 signaling are unable to differentiate into Th2 cells. Using this model, the contribution of specific T cell subsets to the development of fibrosis was evaluated.

METHODS: Intraperitoneal injections of bleomycin were given over 4 weeks to induce pulmonary fibrosis in wildtype mice, mTORC1 null mice, and mTORC2 null mice. Mice were harvested on day 42, and the degree of fibrosis was assessed by histology and pulmonary function testing. Lung inflammatory cells were analyzed by FACS analysis, and cytokine levels were evaluated by ELISA and PCR.

RESULTS: Intraperitoneal bleomycin induces a T cell response characterized by an increase in IL-17A production by both Th17 cells and gamma-delta T cells with no increase in Th2 cells. Mice deficient in mTORC1 had increased mortality and reduced pulmonary function compared to wildtype mice. mTORC1 null mice were unable to produce Th1 and Th17 cells, and did not have an increase in Th2 cells, but did have elevated production of IL-17A via gamma-delta T cells. In contrast, mTORC2 null mice had decreased mortality and less of an impairment in pulmonary function, with increased Th1 cells.

CONCLUSIONS: Our findings indicate that mTORC-dependent differentiation of T cells mediates bleomycin-induced pulmonary fibrosis. Specifically, loss mTORC1 signaling causes increased mortality and fibrosis related to a diminished Th1 response with preserved IL-17A production via gamma-delta T cells, while loss of mTORC2 signaling causes decreased mortality and fibrosis related to an enhanced Th1 response.

TARIK WALKER, MD, MPH / INSTRUCTOR, DIVISION OF PULMONARY MEDICINE / UNIVERSITY OF COLORADO DENVER SCHOOL OF MEDICINE / AURORA, COLORADO, UNITED STATES

Pilot study to assess the feasibility and impact of electronic messaging in patients with ILD

AUTHORS: Tarik Walker; Marvin Schwarz; David Schwartz

GENERAL AUDIENCE SUMMARY

BACKGROUND: Interstitial lung disease (ILD) encompasses a diverse group of chronic lung conditions characterized clinically by distressing dyspnea, fatigue, reduced exercise tolerance and poor health-related quality of life (HRQL). Oxygen therapy, exercise training, and select drugs are prescribed or recommended in hopes of improving outcomes, however there is marked variability in response. The aims of this ongoing pilot project are to assess the feasibility of a weekly, motivational, ILD-relevant text/email messaging intervention and to determine its effect on medical adherence and HRQL.

METHODS/DESIGN: One hundred participants with ILD recruited from two tertiary institutions will be randomized to either the messaging intervention (via short-message-service (SMS) text or email twice monthly for 6 months) or usual care. HRQL, ILD severity, and medical adherence will be measured at baseline, immediately following the intervention, and 6 months after. The primary outcome measures will be change in HRQL and adherence. Subgroup analyses are planned for specific ILD diagnoses (e.g., IPF, connective tissue-related).

RESULTS: To date, 68 subjects have been enrolled: 49 White/16 Hispanic/3 African-American. Their mean age is 63.1 years; 59% are female; 54% are using supplemental oxygen; and 22% are taking medications targeting ILD. Subjects in the intervention group have received an average of 1.5 messages/week. None have reported changing their numbers, losing their phone, or cancelling text service. When participants were asked to verify receiving SMS/email, 85.8% replied via text; 14.2% via email.

DISCUSSION: We anticipate this pilot study will provide evidence to support the feasibility and beneficial role of electronic messaging for patients with ILD. We expect results will inform and optimize the clinical management of these patients and will help shape the conduct of a larger, interventional study.

DISSEMINATING WEEKLY ILD-RELATED EDUCATIONAL & MOTIVATIONAL MESSAGES

Message Topics include:

- ILD risk factors and symptoms
- Value/importance behind medical management adherence
- Stigma reduction
- Responsible behavior
- Communication with family/friends
- Potential access to care/clinics

EXAMPLE TEXTS FROM TEXT LIBRARY:

1)   "Interstitial lung disease is also known as ILD. When was your last visit to your specialist?"

2)   "ILD describes a large group of disorders, most of which cause progressive scarring of lung tissue. Be sure to ask you doctor about any concerns you have about your condition."

3)   "The scarring associated with interstitial lung disease eventually affects your ability to breathe and get enough oxygen into your bloodstream. So make sure you see your doc regularly, wear your oxygen and take your PPI meds!"

4)   "Interstitial lung disease can be caused by long-term exposure to hazardous materials, such as asbestos. In most cases, however, the causes remain unknown."

5)   "Once lung scarring occurs, it's generally irreversible. Medications can slow the damage of interstitial lung disease, so take your meds as often as you can."

6)   "Getting seen for ILD--this is a critical step toward stopping prolonged and worsening symptoms!"

7)   "Using oxygen can't stop lung damage, but it can: Make breathing and exercise easier; Prevent or lessen complications from low blood oxygen levels; Reduce blood pressure in the right side of your heart; and Improve your sleep and sense of well-being."

(GENERIC TEXT TO HELP ENSURE ENGAGEMENT)
"Who won the Broncos v. Ravens? Text 1= Broncos; 2=Ravens; 3=Hate Football!"

TIFFANY WINSTONE, MD / RESPIROLOGY CLINICAL FELLOW, UNIVERSITY OF BRITISH COLUMBIA / VANCOUVER, BRITISH COLUMBIA, CANADA

Frailty is common and associated with dyspnea severity in patients with systemic sclerosis-associated interstitial lung disease

AUTHORS: Tiffany A. Winstone; Joanne M. Kwan; Kathryn Milne; Fran Schooley; James Dunne; Pearce G. Wilcox; Christopher J. Ryerson

GENERAL AUDIENCE SUMMARY

OBJECTIVES: Frailty is defined as the accumulation of deficits that decrease the ability to tolerate and respond to biologic stress. Patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD) frequently have multiple symptoms, co-morbidities, and disabilities that can be summarized by the construct of frailty. Frailty has been studied in healthy and chronic disease populations but has not been characterized in patients with SSc-ILD. We studied a cohort of SSc-ILD patients to determine the prevalence of frailty in this population and to identify variables that predict frailty severity.

METHODS: A 42-item patient-reported Frailty Index was completed by consecutive patients recruited from a specialized SSc-ILD clinic. The proportion of deficits was calculated as previously described (e.g. 10 deficits reported out of 42 surveyed = Frailty Index of 10/42 = 0.24). Approximately 10% of Canadian adults >65 years old are considered frail, previously defined by a Frailty Index >0.21. Additional clinical parameters were extracted from medical records and a self-reported study questionnaire, including lung function and dyspnea score (University of California San Diego Shortness of Breath Questionnaire [UCSD SOBQ]). Bivariate and multivariate analyses were used to identify predictors of frailty.

RESULTS: 59 patients with SSc-ILD were included. The mean age was 59 years, 75% were women, and most patients had mild-to-moderate lung function impairment (mean FVC 79%-predicted and DLCO 55%-predicted). The mean Frailty Index was 0.25 ± 0.15, with 61% of the study population meeting the criteria for frailty (Figure 1). Body mass index, smoking history, dyspnea score, and DLCO predicted frailty on bivariate analysis (Table 1). Dyspnea score had the strongest association with Frailty Index ($r = 0.42$, $p = 0.02$), and was the only variable independently associated with Frailty Index on multivariate analysis.

CONCLUSIONS: Patients with SSc-ILD have a high prevalence of frailty. The perception of dyspnea had a more important role in predicting frailty than age and lung function. Additional studies are required to determine whether frailty can be used to improve prognostication and to identify patients unlikely to tolerate potentially toxic pharmacotherapy.

XIAOPING WU / FELLOW, INTERNAL MEDICINE / NEW YORK – PRESBYTERIAN / WEILL CORNELL MEDICAL COLLEGE / NEW YORK, NEW YORK, UNITED STATES

The clinical utility of a molecular diagnostic in differentiating idiopathic pulmonary fibrosis from other interstitial lung diseases

AUTHORS: Xiaoping Wu; Michael Rosenbluth; Yoonha Choi; Sherry Danese; Kevin Flaherty; Fernando Martinez

GENERAL AUDIENCE SUMMARY

OBJECTIVES: The accurate diagnosis of idiopathic pulmonary fibrosis (IPF) continues to be challenging due to its overlapping features with other interstitial lung diseases (ILDs). With the approval of pirfenidone and nintedanib for treatment of IPF, there is greater urgency to identify patients with IPF without requiring surgical lung biopsy (SLB). In this study we evaluated the clinical utility of a genomic classifier under development to identify usual interstitial pneumonia (UIP), the pathology pattern associated with IPF, using bronchoscopically collected samples.

METHODS: A national survey was conducted from March 17–20, 2015 among 76 pulmonologists from ILD centers and non-specialty clinics. The survey described a genomic test with high specificity for ruling in UIP pattern using bronchoscopically collected samples. Physicians were asked about diagnostic/treatment next steps on four ILD patient cases (confident UIP, possible UIP, possible UIP versus hypersensitivity pneumonitis (HP), connective tissue disease related ILD) and how this genomic test would alter management.

RESULTS: Physicians' likelihood of using the genomic test varied with the method of sampling. Ninety-one percent of physicians reported they would likely use the test if it required bronchoalveolar lavage (BAL), compared with 85% for transbronchial biopsy (TBB), and 63% for SLB. Across four clinical scenarios, a positive genomic test result significantly increased treatment with pirfenidone/nintedanib and reduced biopsies. The largest impact occurred in the possible UIP cases with an increase in treatment from 11% to 46% (p<0.001) and a decrease in biopsies from 59% to 26% (p<0.001) (Figure 1B and 1C). A positive test in the setting of confident UIP raised treatment recommendation from 47% to 70% (p<0.001) and decreased biopsies from 42% to 18% (p<0.001), suggesting its utility even in cases with high pre-test probability for UIP. A negative test result was less impactful on management than a positive one (Figure 2).

CONCLUSIONS: The introduction of an innovative genomic diagnostic test had strong clinical impact on management approaches for ILD. Utilization of such diagnostic tools may decrease the need for biopsies and increase appropriate diagnosis and treatment of IPF.

Figure 1. Impact of a positive genomic test result on diagnostic / treatment plan (90% PPV)
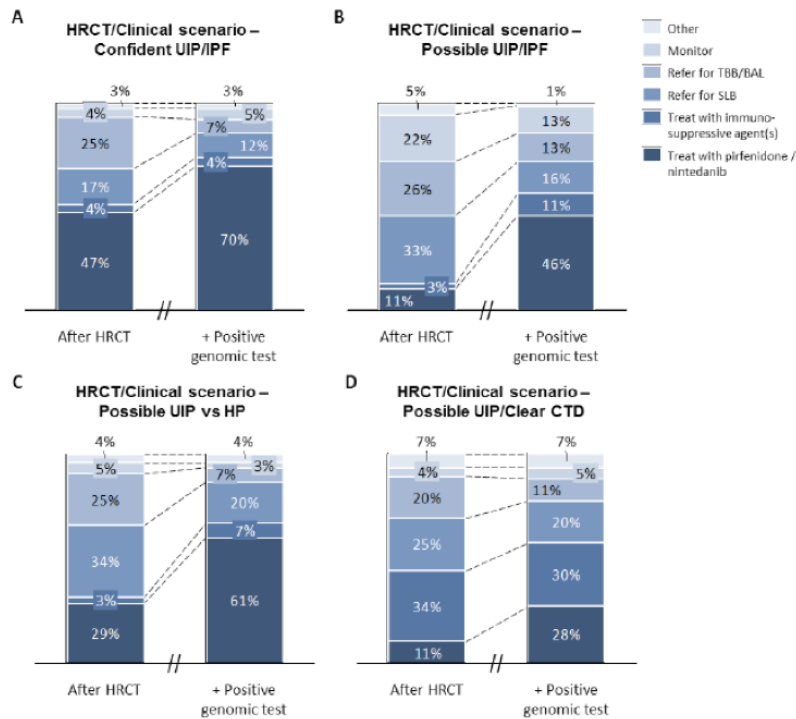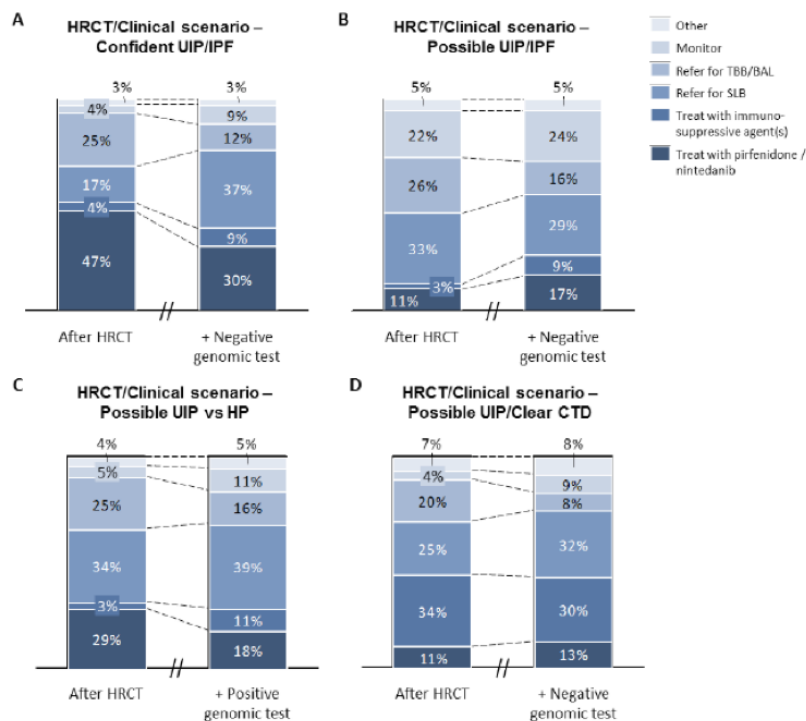
Figure 2. Impact of a negative genomic test result on diagnostic / treatment plan (80% NPV)

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WIM A. WUYTS, MD, PHD / PROFESSOR, DEPARTMENT OF RESPIRATORY MEDICINE / UNIVERSITY HOSPITALS LEUVEN / LEUVEN, BELGIUM

Efficacy and safety of nintedanib in patients with idiopathic pulmonary fibrosis (IPF) and forced vital capacity (FVC) ≤50% predicted

AUTHORS: Wim A Wuyts[1], Martin Kolb[2], Susanne Stowasser[3], Toshio Kimura[3], Ganesh Raghu[4], John T Huggins[5]

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2 McMaster University, Hamilton, Canada
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GENERAL AUDIENCE SUMMARY

OBJECTIVES: The INPULSIS® trials assessed the efficacy and safety of nintedanib 150 mg twice daily (bid) in patients with IPF. Compared with placebo, nintedanib reduced the rate of decline in FVC in both trials. Patients who completed the 52-week treatment period and follow-up visit 4 weeks later in an INPULSIS® trial could receive open-label nintedanib in an extension trial (INPULSIS®-ON). Patients with FVC <50% predicted were excluded from the INPULSIS® trials, but could participate in INPULSIS®-ON. We assessed the effect of nintedanib in patients with FVC ≤50% and >50% predicted at the start of INPULSIS®-ON.

METHODS: Patients treated with placebo in INPULSIS® initiated treatment with nintedanib in INPULSIS®-ON (n=304); patients treated with nintedanib continued to receive nintedanib (n=430). A *post-hoc* interim subgroup analysis of patients with baseline FVC ≤50% versus >50% predicted at the start of INPULSIS®-ON was undertaken.

RESULTS: 41 and 690 patients treated in INPULSIS®-ON had baseline FVC ≤50% and >50% predicted, respectively. For patients with FVC ≤50% predicted, mean age was 66.9 years, 70.7% were White, mean FVC was 1602 mL. For patients with FVC >50% predicted, mean age was 67.1 years, 58.1% were White, mean FVC was 2683 mL. Mean (SD) duration of exposure in INPULSIS®-ON was 12.1 (8.6) and 17.0 (6.8) months in patients with baseline FVC ≤50% and >50% predicted, respectively. In patients with baseline FVC ≤50% predicted, the absolute mean change from baseline in FVC at week 48 was −62.3 mL while in patients with baseline FVC >50% predicted, it was −87.9 mL (compared with a mean change from baseline to week 52 in the INPULSIS® trials of −88.9 mL). Consistent results were observed for changes from baseline in FVC over time (Figure). The most frequent adverse events by subgroup are shown in the table.

CONCLUSION: In INPULSIS®-ON, the decline in FVC in patients with baseline FVC ≤50% and >50% predicted was similar to that in patients treated with nintedanib in INPULSIS®, caution as analyses were exploratory and the number of patients with baseline FVC ≤50% predicted was small.
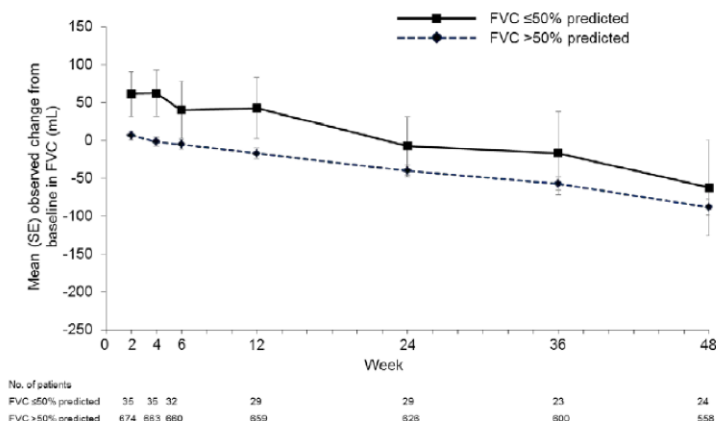
N (%)	INPULSIS®		INPULSIS®-ON	
	Nintedanib (n=638)	Placebo (n=423)	FVC ≤50% predicted (n=41)	FVC >50% predicted (n=690)
Diarrhea	398 (62.4)	78 (18.4)	19 (46.3)	446 (64.6)
Nausea	156 (24.5)	28 (6.6)	7 (17.1)	111 (16.1)
Cough	85 (13.3)	57 (13.5)	7 (17.1)	114 (16.5)
Nasopharyngitis	87 (13.6)	68 (16.1)	3 (7.3)	100 (14.5)
Bronchitis	67 (10.5)	45 (10.6)	4 (9.8)	97 (14.1)
Dyspnea	49 (7.7)	48 (11.3)	10 (24.4)	88 (12.8)
Progression of IPF*	64 (10.0)	61 (14.4)	14 (34.1)	104 (15.1)
Decreased appetite	68 (10.7)	24 (5.7)	3 (7.3)	73 (10.6)
Weight decreased	62 (9.7)	15 (3.5)	7 (17.1)	36 (11.8)
Vomiting	74 (11.6)	11 (2.6)	2 (4.9)	66 (9.6)

Adverse events reported in >10% of patients in any treatment group in INPULSIS® or INPULSIS®-ON.

*Corresponds to MedDRA term 'IPF', which included disease worsening and IPF exacerbations.

GUOYING YU, PHD / ASSOCIATE RESEARCH SCIENTIST, SECTION OF PULMONARY, CRITICAL CARE AND SLEEP MEDICINE / YALE UNIVERSITY SCHOOL OF MEDICINE / NEW HAVEN, CONNECTICUT, UNITED STATES

Thyroid hormone as a novel therapeutic agent in lung fibrosis

AUTHORS: Guoying Yu[1], Argyris Tzouvelekis[1], Jose Herazo-Maya[1], Rong Wang[1], Joao Pedro Saar Werneck de Castro[2], Rafael Arrojoe Drigo[2], Robert Homer[3], Anup Srivastava[1], Praveen Mannam[1], Antonio Carlos Bianco[2], Naftali Kaminski[1]

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GENERAL AUDIENCE SUMMARY:

BACKGROUND: Idiopathic pulmonary fibrosis (IPF) is a devastating chronic lung disease with yet unknown etiology and treatment ineffective.

OBJECTIVE: To delineate the role of thyroid hormones in pulmonary fibrosis

METHODS AND RESULTS: Microarray gene expression analysis in control (n=43) and IPF (n=89) lungs demonstrated that Iodothyronine Diodinase 2 (DIO2), an enzyme that catalyzes the conversion of T4 to active T3, was one of the most significantly upregulated genes that differentiated patients with IPF from controls (8.49, p<0.0001). Data was further validated on a protein and enzymatic activity level (p<0.05). DIO2 knockout mice developed more severe fibrosis after intratracheal administration of bleomycin compared to wild type ones, as assessed by Ashcroft score and hydroxyproline assay (p<0.05). Similarly, administration of propylthiouracil (PTU), an inhibitor of both T4 and T3 enhanced bleomycin induced fibrosis. Intraperitoneal delivery of T4 (40mg/kg) at days 3, and 7 following bleomycin exposure attenuated the fibrotic process as measured by hydroxyproline, Ashcroft score and masson tricrome staining. Finally, aerosolized administration of T3 at dose of 40μg/kg also led to a statistically significant blunting of bleomycin induced increases of hydroxyproline and T3 treated mice exhibited prolonged survival compared to controls (p=0.0007, HR:6.3080, CI:2.3268 to 17.1009). Follow up metabolic studies revealed TH exerts its therapeutic effects through upregulation of peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1a) leading to restoration of bleomycin-driven mitochondrial abnormalities. PGC-1a knockout mice exhibited enhanced fibrotic response to bleomycin, suggesting a protective role for PGC-1a in experimental lung fibrosis. We conclude that TH treatment is protective against fibrotic lung injury through restoration of AECs' mitochondrial biogenesis, rescuing them from bleomycin-induced apoptosis. DiO2 upregulation may represent a compensatory response that makes more TH available to the injured lung.

CONCLUSIONS: Taken together, our data indicate that inhibition of thyroid hormone enhances lung fibrosis and local administration of aerosolized thyroid hormone blunts experimental lung fibrosis. Further studies with regard to the impacts of this potential intervention in humans are suggested.

ANA C. ZAMORA, MD / PULMONARY AND CRITICAL CARE SENIOR FELLOW / MAYO CLINIC / ROCHESTER, MINNESOTA, UNITED STATES

The Palliative Effect of Amniotic Membrane Derived Cells (AMDC) and Conditioned Media on Lung Fibrosis

AUTHORS: Ana C. Zamora[1], MD, Deanne M. Hebrink[2], Paige E. Jenson[2], Theodore J. Kottom[2], PhD, Andrew H. Limper[1,2] MD

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GENERAL AUDIENCE SUMMARY

BACKGROUND/OBJECTIVE: Idiopathic Pulmonary Fibrosis is a chronic progressive disease with a dismal prognosis and no effective therapy. New treatments are needed. Prior studies showed that surgery performed in utero, results in fetal healing without scar formation suggesting amniotic fluid might promote a healing with a "scarless" phenotype. Recently, there have been several manuscripts indicating AMDC may be successfully employed to treat fibrotic diseases. We hypothesize that AMDC-conditioned media will reduce the fibrotic potential of human fibroblasts (IMR-90) despite stimulation with TGF-ß1.

METHODS: IMRs-90 were incubated with AMDC-conditioned media after stimulation with TGF-ß1. Measure of fibronectin by PCR/ELISA was performed after 24 hours. Serum free media and conditioned media derived from epithelial cells was control group. We dialyzed and fractionated the AMDC-conditioned media (10 kDa and 3 kDa membranes) to characterize the molecular size of soluble factor(s) responsible for the inhibitory effect. We measured cytokines, and growth factors using multiplex ELISA. Finally, we employed indomethacin treatment of the AMDC cultures to assess the potential roles of prostaglandins in this phenotype.

RESULTS: There was a suppression of fibronectin expression in the IMR-90 treated with AMDC-conditioned media despite stimulation with TGF-ß1; this phenomena was not observed in the control groups. (Figure 1 panel A). After dialyzing the AMDC-conditioned media the suppression of fibronectin expression was no longer observed. (Figure 1 Panel B). Levels of IL-1b,IL-2, IL-4,IL-5,IL-6,IL-8, IL-10,GM-CSF,IFN-g, and TNF-a by multiplex ELISA were lower in the AMDC-conditioned media compared with the control. Addition of indomethacin to the AMDC-conditioned media neutralized the observed inhibitory fibrotic effect of AMDC-conditioned media.(Figure 2).

CONCLUSIONS: AMDC-conditioned media demonstrated suppression of fibronectin expression of IMR-90 despite stimulation with TGF-ß1 supporting a potential therapeutic role in lung fibrosis. We presumed the molecules responsible for the inhibitory effect are less than 3 kDa. Since the fibrotic inhibitory effect was lost after the addition of indomethacin a role of prostaglandins and related molecules is highly suspected.

Figure 1. Panel A. Real time PCR shows suppression of fibronectin expression in the IMR-90 treated with AMDC-conditioned media despite stimulation with TGF-β1. **Panel B.** PCR- real time shows after dialyzing the AMDC-conditioned media the suppression of fibronectin expression in IMR-90 was no longer observed.
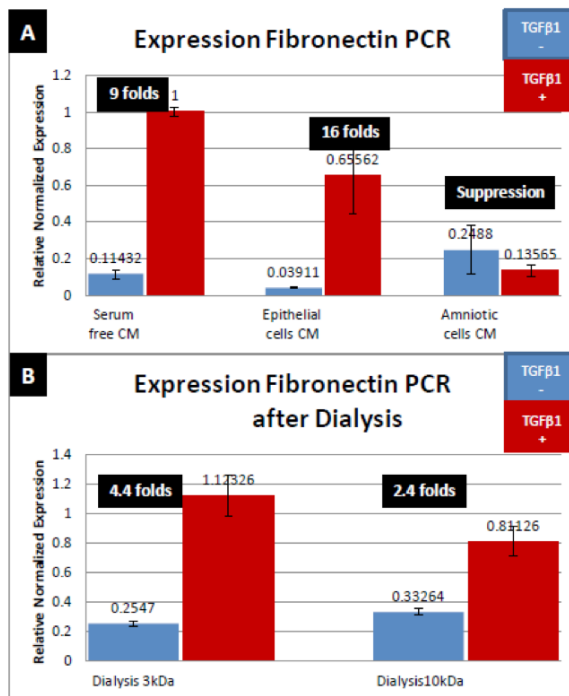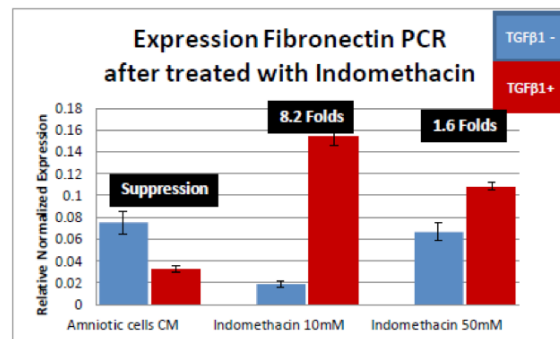
Figure 2. Real time PCR shows the addition of indomethacin to the AMDC-conditioned media neutralized the inhibitory fibrotic effect of AMDC-conditioned media on suppressing fibroblast expression of fibronectin.

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industry 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 industry researchers to submit abstracts of their scientific research for poster presentation at the *PFF Summit 2015: From Bench to Bedside.*

Subject matter deemed appropriate for poster presentation at the *PFF Summit 2015* 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.

JAN DE BACKER, PHD / CEO / FLUIDDA / KONTICH, BELGIUM

Comparison of IPF Disease Pathology to Healthy Subjects using Functional Respiratory Imaging

AUTHORS: Wim Vos; Cedric Van Holsbeke; Francisca Ferreira; Lieven Nuyttens; Thomas O'Riordan; Jan De Backer; Wilfried De Backer

GENERAL AUDIENCE SUMMARY

OBJECTIVE: Currently, reliable and objective parameters that allow diagnosing idiopathic pulmonary fibrosis (IPF) and assessing the effect of interventions are poorly defined and not fully validated. Forced vital capacity (FVC) is the most commonly employed and accepted endpoint in clinical trials of IPF to date however there is a lack of sensitivity in spirometry-based endpoints. Better biomarkers linking regional lung characteristics to clinical outcomes are therefore needed. This study aims to demonstrate that Functional Respiratory Imaging (FRI) provides regional information of IPF disease manifestation and hence can distinguish healthy from diseased lungs.

METHODS: In this trial high resolution computed tomography (HRCT) scans of 4 IPF patients were studied and compared to geometry-matched healthy volunteers. Scans were taken at total lung capacity (TLC). Using FRI, measurements of lobe volumes, airway wall volume and airway radius were performed. In addition the quantification and visualization of the blood vessel density and fibrosis was also implemented.

RESULTS: The results showed that the IPF patients have a significantly higher FRI fibrosis parameter (p=0.037) with 15.80±11.63% of the lobe in comparison to 3.71±0.96% of the lobe in the healthy group (see figure). A significant increase (p=0.013) was also observed in the specific airway radius from 0.14±0.06cm/L to 0.26±0.11cm/L, which can be explained by traction bronchiectasis. Furthermore significantly (p=0.002) smaller lobe volumes were observed in the IPF patients. While the healthy cohort had an average lobe volume of 97.62±17.11%pred, the IPF cohort had an average lobe volume of 60.55±20.05%pred. Finally a trend (p=0.096) towards larger specific airway wall volumes in the IPF cohort can be seen with an airway wall volume of 5.40±1.47ml/L and 10.54±6.83ml/L for the healthy subjects and IPF subjects respectively.

CONCLUSIONS: FRI appears to be a sensitive tool which provides detailed regional information. In this study FRI allowed to distinguish healthy lungs from lungs affected by IPF. These results could lead to the development of a biomarker to track disease progression and to assess the effect of the interventions. These topics will be subject of future research.
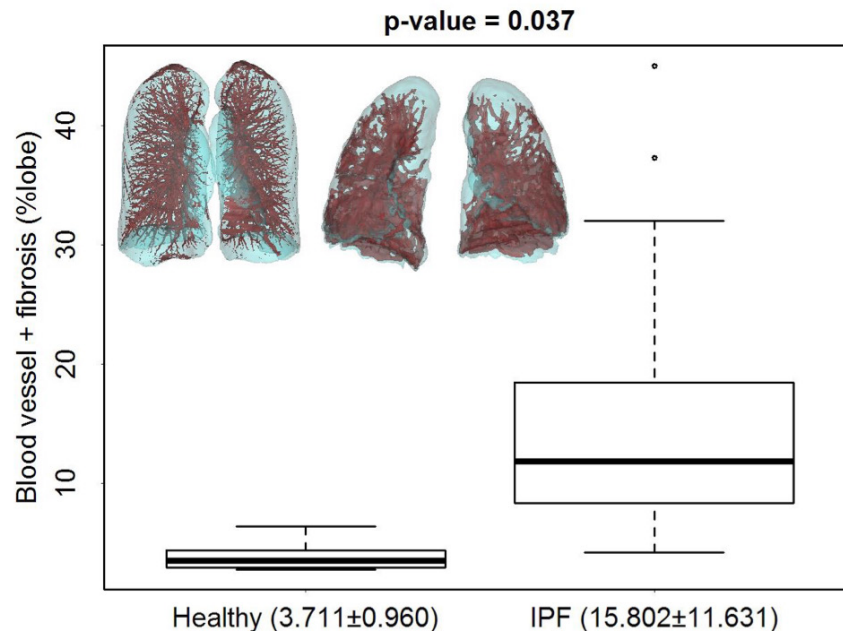
p-value = 0.037

JAN DE BACKER, PHD / CEO / FLUIDDA / KONTICH, BELGIUM

Assessment of Regional Lung Deposition of Aerosol Aerodone in Idiopathic Pulmonary Fibrosis Patients using Functional Respiratory Imaging

AUTHORS: Francisca Ferreira[1], Wim Vos[1], Cedric Van Holsbeke[1], Lieven Nuyttens[2], Jan De Backer[1], Mark W. Surber[3], Wilfried De Backer[4]

1 FLUIDDA NV

2 FLUIDDA Inc.

3 Genoa Pharmaceuticals Inc.

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GENERAL AUDIENCE SUMMARY

OBJECTIVES: Idiopathic pulmonary fibrosis (IPF) is a progressive fibrotic disease characterized by irreversible loss of lung function. Two oral drugs were recently approved for IPF; Ofev® (nintedanib) and Esbriet® (pirfenidone). Large oral doses for each drug result in significant, but only limited slowing of IPF disease progression. Associated side effects prevent dose escalation for additional efficacy, challenge patient compliance and impede combination therapy. By inhalation, small doses result in large local lung levels with limited systemic exposure. It is predicted that inhalation will improve medication efficacy, safety and tolerability. In IPF, disease severity may reduce access of an inhaled aerosol to desired peripheral regions. Functional Respiratory Imaging (FRI) was used to measure the effect of breathing pattern on inhaled aerosol pirfenidone (Aerodone™) regional lung deposition in patients of various IPF disease severities.

METHODS: In this study, three-dimensional geometries of 3 IPF patients were selected according to disease severity; mild (83%pFVC), moderate (60%pFVC) and severe (42%pFVC). An average upper airway was digitally coupled to the patient-specific intrathoracic region. Using FRI, the fraction of delivered dose reaching different lung regions was assessed. Two breathing patterns were simulated (Figure 1): a trained profile (Inhalation volume: 0.8L, Respiratory rate: 7.5bpm, Inspiration/Expiration ratio: 1.67) and an average IPF profile (Inhalation volume: 0.8L, Respiratory rate: 20bpm, Inspiration/Expiration ratio: 0.85). Two Aerodone formulations (4 mg/mL and 15 mg/mL) were studied.

RESULTS: The trained IPF breathing profile resulted high intrathoracic exposure (~64%) and high peripheral lung deposition (>35%). Less than 7% was exhaled. Employing the average IPF breathing profile, lower intrathoracic (~42%) and peripheral (~16%) deposition was observed with a higher exhaled fraction (~12%). Total intrathoracic deposition was not influenced by disease severity. However, disease severity did correlate with increased upper lobe and peripheral airway deposition. No differences were observed between the two formulations (Figure 2).

CONCLUSIONS: This study showed that efficient peripheral aerosol deposition is possible in IPF patients with varying disease severity. Results also demonstrate that optimizing patient breathing pattern improves total and peripheral aerosol deposition in the IPF lung. Disease severity did not influence total intrathoracic deposition, although differences were observed at a regional level.
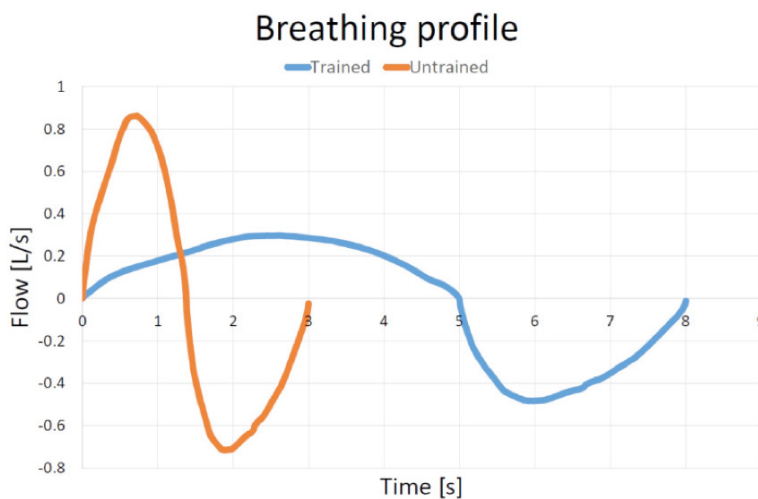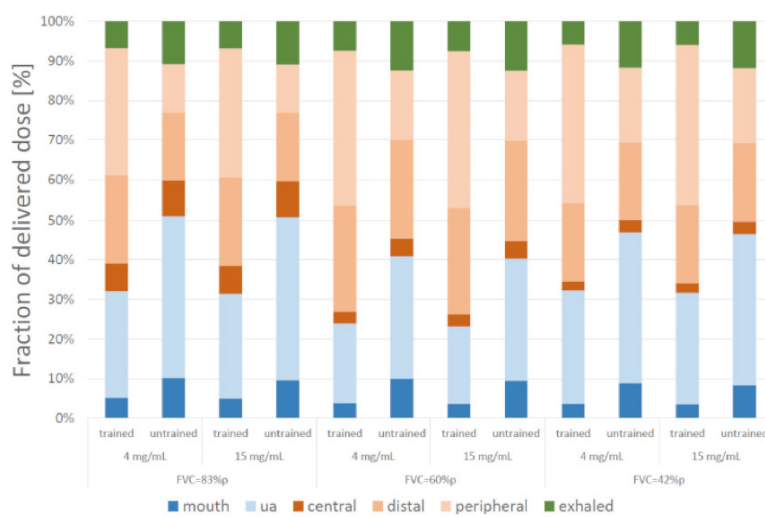
MARK FISHER, BSC / SENIOR DIRECTOR, INTERMUNE, INC (A WHOLLY OWNED ROCHE SUBSIDIARY) /
GENENTECH/ROCHE / LONDON, UNITED KINGDOM

Disease progression modeling in idiopathic pulmonary fibrosis: a prediction of time to disease progression and life expectancy with pirfenidone

PRESENTER: Cheryl Fattman, PhD

AUTHORS: Mark Fisher[1], Toby Maher[2], Paul Dolan[3], Christian Hill[4], Jade Marshall[4]

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GENERAL AUDIENCE SUMMARY

OBJECTIVES: Clinical trials in idiopathic pulmonary fibrosis (IPF) are currently not designed to estimate disease progression and survival over a long period of time, since most trials only collect outcomes up to 12 months. The objectives of this study were to create a disease progression model over a lifetime and to predict the extent to which treatment with pirfenidone could extend the time to disease progression and improve life expectancy compared with best supportive care in patients with IPF.

METHODS: A partitioned survival model was developed to characterize disease progression by four health states: progression-free; progressed; lung transplant; and dead. The proportion of patients in each health state was calculated every 3 months based on parametric survival distributions fitted to Kaplan-Meier data from clinical trials and registries. Distributions calculating progression-free survival (PFS) and overall survival (OS) for pirfenidone were fitted to data from the randomized placebo-controlled trials of pirfenidone (ASCEND and CAPACITY) and a long-term extension study (RECAP). For best supportive care, the placebo arm of the trials and a US-based IPF registry enrolling patients from the National Jewish Health Interstitial Lung Disease database were used. Mean PFS and OS were determined for pirfenidone and best supportive care. Uncertainty was explored by deterministic and probabilistic sensitivity analysis.

RESULTS: The model calculated mean PFS as 3.278 years and 2.182 years with pirfenidone and best supportive care, respectively. Hence, pirfenidone extended the estimated mean time to disease progression by 1.096 years. Mean OS was calculated as 9.289 years and 6.099 years with pirfenidone and best supportive care, respectively. Therefore, pirfenidone improved estimated life expectancy compared to best supportive care by 3.190 years. The extent to which pirfenidone improved PFS and OS was sensitive to the choice of parametric survival distribution and method of extrapolation.

CONCLUSION: These conclusions are consistent with expectations for a therapy that has been shown to reduce disease progression and mortality, as measured by a pooled analysis of outcomes in Phase 3 clinical trials at 52 weeks.

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PFF
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FROM BENCH 2015
TO BEDSIDE

.... 161

XIN GENG / SCIENTIST, BIOLOGY / GLOBAL BLOOD THERAPEUTICS / SOUTH SAN FRANCISCO, CALIFORNIA, UNITED STATES

Effects of GBT1118, A Potent Allosteric Modifier of Hemoglobin Oxygen Affinity, on Bleomycin-Induced Murine Model of Hypoxemia and Lung Fibrosis

AUTHORS: Xing Geng, Kobina Dufu, Qing Xu, Athiwat Hutchaleelaha

GENERAL AUDIENCE SUMMARY

OBJECTIVES: Although hypoxia is a prominent clinical feature of Idiopathic Pulmonary Fibrosis (IPF), no drug currently available could treat exertional breathlessness — the most clinically relevant symptom in IPF patients. GBT1118 is a novel orally-bioavailable small molecule that binds to hemoglobin (Hb) and produces a concentration-dependent left shift in the oxygen equilibrium curve with subsequent increase in Hb-oxygen affinity and arterial oxygen loading. Previously we reported increased Hb oxygen affinity by GBT1118, which resulted in improved tissue oxygenation and enhanced survival during severe hypoxia (5% inspired oxygen). Here we investigated whether GBT1118 could ameliorate hypoxemia associated with lung fibrosis induced by bleomycin in mice.

METHODS: GBT1118 was evaluated in the bleomycin-induced lung fibrosis model. Bleomycin (3 units/kg) or saline control was administered to C57BL6 mice via oropharyngeal aspiration on day 0. After pulmonary fibrosis and hypoxemia were induced by day 7, mice were then treated with vehicle control or two different dose levels of GBT1118 via oral administration (PO) for eight consecutive days, from day 8 to day 15 (n=12 each group). Mice were weighed daily and sacrificed on day 15. Arterial blood gases and oxygen saturation were measured on day 7 and day 14. Bronchoalveolar lavage fluid (BALF) was analyzed for leukocyte cell count and collagen quantification. Lung tissues were analyzed for fibrosis by histopathology.

RESULTS: Mice treated with bleomycin developed significant weight loss, hypoxemia (decrease in the arterial oxygen saturation), reduced respiratory functions, elevations in BALF inflammatory cell counts, and collagen deposition in lung tissue. In contrast, bleomycin mice treated with GBT1118 showed strong anti-hypoxemic effects with significantly improved arterial oxygen saturation, respiratory functions, increased body weight, and reductions in BALF inflammatory cell counts.

CONCLUSION: These findings suggest that hemoglobin modifiers such as GBT1118 represent a promising and novel therapeutic strategy for treatment of hypoxemia associated with chronic fibrotic lung disorders, including IPF. GBT440, an analogue of GBT1118, is currently in clinical trials for the treatment of sickle cell disease.

JING HUANG, PHD / VP OF BIOINFORMATICS, DIVISION OF RESEARCH AND DEVELOPMENT / VERACYTE, INC. / SOUTH SAN FRANCISCO, CALIFORNIA, UNITED STATES

Diagnosis of Idiopathic Pulmonary Fibrosis: Classifying the Usual Interstitial Pneumonia Pattern in Transbronchial Biopsies Using Machine Learning

AUTHORS: Huang, J.; Choi, Y.; Lin, B.; Pankratz, D.G.; Colby, T.V.; Myers, J.L.; Fedorowicz, G.; Conley, C.J.; Imtiaz, U.; Kennedy, G.C.
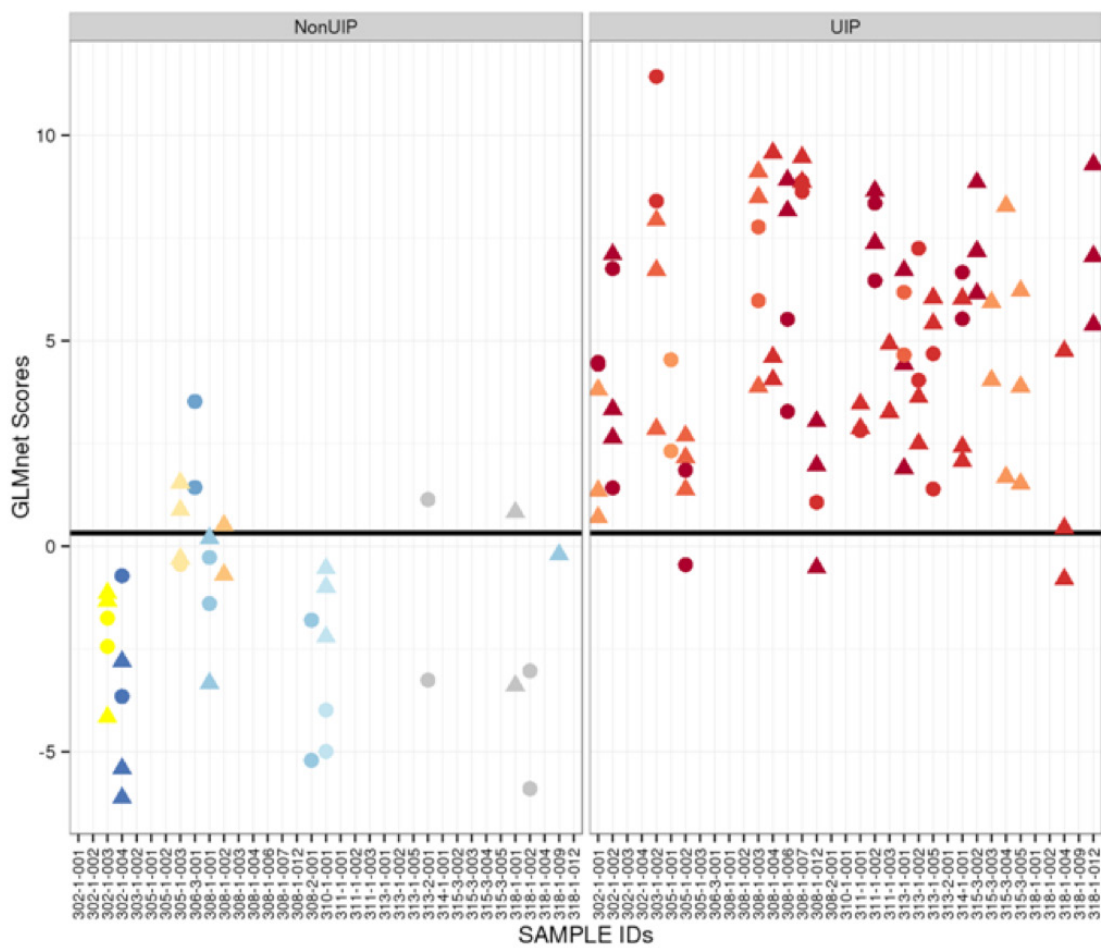
GENERAL AUDIENCE SUMMARY

OBJECTIVES: Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fibrotic lung disease of unknown cause and poor prognosis. Distinguishing IPF from other idiopathic interstitial pneumonias (IIP) requires review of clinical, radiological, and histopathological features by physician experts. The usual interstitial pneumonia (UIP) pattern, evident either by high-resolution CT or by pathology, is a hallmark of IPF. Our goal is to develop a molecular test that distinguishes UIP from other pathology patterns (non-UIP) with high confidence, using a less invasive transbronchial biopsy (TBB).

METHODS: We developed classifiers to distinguish UIP from non-UIP pathology patterns using whole-transcriptional microarray data from 135 TBB samples (40 patients). A subset of samples (19 TBB samples from 12 patients) was repeated using deep RNAseq data. For training and classification, we define non-specific interstitial pneumonia, unclassifiable fibrotic ILD, emphysema, organizing pneumonia, respiratory bronchiolitis and sarcoidosis pathology as non-UIP. We assign UIP labels to samples with UIP, classic UIP, difficult UIP or favor UIP pathology. Microarray data classifiers were trained using different numbers of genes, and in some cases, inclusion of clinical variables. Classifier performance was evaluated by leave-one-patient-out (LOPO) cross-validation. We also investigated the classification of unclassifiable fibrotic ILD (favor HP, favor UIP and "no preference" pathology).

RESULTS: By LOPO cross-validation, logistic regression with Lasso penalty distinguishes UIP from non-UIP with areas under the ROC curve (AUC) above 0.85. RNAseq data on a reduced sample set gives similar results, demonstrating a platform independent signal. When "no preference" samples are excluded from training, the classifier achieved an AUC of 0.93. Favor HP and favor UIP unclassifiable ILD samples consistently classify as non-UIP and UIP, respectively; "no preference" samples show an inconsistent classification pattern. Inclusion of clinical variables (age, smoking history and gender) further improves performance to an AUC of 0.97 (See Figure).

CONCLUSION: TBB classification using gene expression shows potential as a pathology surrogate. Our results with unclassifiable fibrotic ILDs.

ANDY LUBER, PHARMD / VP, CLINICAL PHARMACOLOGY / MOERAE MATRIX, INC. / MORRISTOWN, NEW JERSEY, UNITED STATES

Phase 1 Evaluation of Safety, Tolerability, and Pharmacokinetics (PK) of The MAPKAP Kinase II (MK2) Inhibitor, MMI-0100, When Given Via Inhalation (IH) in Healthy Volunteers

AUTHORS: Andrew Luber; William Bradford; Caryn Peterson; Colleen Brophy; Alyssa Panitch; Cynthia Lander

GENERAL AUDIENCE SUMMARY

OBJECTIVES: MMI-0100 is a potent and selective cell-permeant peptide inhibitor of MK2, an important mediator of both fibrosis and inflammation. Preclinical evaluations of MMI-0100 have demonstrated strong anti-fibrotic activity in 8 distinct animal models and an excellent safety/tolerability profile when administered via IH. Direct administration to target lung tissue and rapid cellular uptake of MMI-0100 at the site of delivery minimize systemic exposure. The Phase 1 program evaluated the safety/tolerability and PK of IH MMI-0100 in healthy volunteers.

METHODS: Double blind (DB), randomized, single ascending dose (SAD) IH study in healthy volunteers, evaluating safety, tolerability and plasma PK (0-8hrs; LLQ: 3.91ng/mL) of MMI-0100 or matching placebo at 0.75, 1.5, 3, 6, 12, 24 or 40mg doses.

RESULTS: 48 subjects were enrolled (median age, range): 23 yrs (18-54), 46% Male. MMI-0100 was well tolerated, with no drug-related Grade 3 or 4 adverse events, SAEs, or dose limiting toxicities reported. 24 subjects (50%) experienced at least 1 adverse event with only mild cough in a single subject in Cohort 1 (0.75mg), Cohort 6 (24mg) and Cohort 7 (40mg) being attributed to treatment initiation. There were no abnormal clinical observations. Little to no plasma MMI-0100 concentrations were observed, with only 2 subjects in the highest dosing group (Cohort 7 (40mg)) having measurable levels slightly above LLQ (4-7ng/mL). Available data from ongoing Phase 1 clinical trials will be presented.

CONCLUSIONS: MMI-0100 was well tolerated in the SAD trial, even at >17x the anticipated therapeutic dose. This, together with the strong anti-fibrotic activity observed in multiple animal models of fibrosis and direct delivery, with rapid cellular uptake by target lung tissues, makes MMI-0100 a promising candidate for further evaluation for treatment of fibrotic lung disease.

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FROM BENCH 2015
TO BEDSIDE

165

STEVEN D. NATHAN, MD / MEDICAL DIRECTOR, PULMONARY DIVISION, LUNG TRANSPLANT AND ADVANCED LUNG DISEASE PROGRAM / INOVA FAIRFAX HOSPITAL / FALLS CHURCH, VIRGINIA, UNITED STATES

Effect of pirfenidone on all-cause mortality in patients with idiopathic pulmonary fibrosis (IPF): comparison of pooled analysis with meta-analysis from the ASCEND and CAPACITY trials

PRESENTER: Edward Mannix, PhD

AUTHORS: Steven D. Nathan[1], Carlo Albera[2], Williamson Z. Bradford[3], Ulrich Costabel[4], Monica Daigl[5], Ian Glaspole[6], Marilyn K. Glassberg[7], Klaus-Uwe Kirchgaessler[5], Lisa H. Lancaster[8], David J. Lederer[9], Paul W. Noble[10], Carlos A. Pereira[11], Jeffrey J. Swigris[12], Dominique Valeyre[13]

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 5 Roche, Basel, Switzerland
 6 Alfred Hospital and Monash University, Melbourne, Australia
 7 University of Miami Miller School of Medicine, Miami, Florida, United States
 8 Vanderbilt University Medical Center, Nashville, Tennessee, United States
 9 Columbia University Medical Center, New York, New York, United States
10 Cedars-Sinai Medical Center, Los Angeles, California, United States
11 Paulista School of Medicine, Federal University of São Paulo, São Paulo, Brazil
12 National Jewish Health, Denver, Colorado, United States
13 Assistance Publique-Hôpitaux de Paris, Avicenne University, Bobigny, France

GENERAL AUDIENCE SUMMARY

OBJECTIVES: The effect of pirfenidone on all-cause mortality (ACM) was determined in patients with IPF from the ASCEND (PIPF-016) and CAPACITY (PIPF-004/-006) Phase 3 trials at weeks 52, 72 and through the end of study. We compared results of pooled and meta-analyses for ACM at all three time points.

METHODS: The patient population (N=1247) from the ASCEND and two CAPACITY trials were used to assess ACM. The results from the 3 trials were combined through pooled and meta-analyses. Pooled analysis was stratified by study. For random-effects meta-analysis, study heterogeneity was assessed by the DerSimonian and Laird method.

RESULTS: In the pooled analysis, patients who received pirfenidone had a 48% relative reduction in the risk of ACM within 52 weeks compared with patients in the placebo group. ACM occurred in 22/623 (3.5%) patients in the pirfenidone group compared with 42/624 (6.7%) in the placebo group (HR 0.52; 95% CI 0.31–0.87; P=0.0107). Over the 72 weeks following randomization, a 37% relative reduction in the risk of death was observed among patients receiving pirfenidone compared with placebo (32/623 [5.1%] vs 50/624 [8.0%]; HR 0.63; 95% CI 0.41–0.98; P=0.0404). In the end-of-study analysis, a consistent trend over time was observed to week 120; the relative reduction in ACM risk was 31% favoring pirfenidone (38/623 [6.1%]) compared with placebo (54/624 [8.7%]; HR 0.69; 95% CI 0.46–1.05; P=0.0789). For the meta-analysis, the relative reduction in risk of ACM for patients in the pirfenidone compared with those in the placebo group at weeks 52, 72 and through end of study was 48%, 36% and 31%, respectively (week 52: HR 0.52; 95% CI 0.31–0.88; P=0.0138; week 72: HR 0.64; 95% CI 0.41–0.99; P=0.0459; end of study: HR 0.69; 95% CI 0.46–1.05; P=0.0861). There was no evidence of heterogeneity between studies in the three analyses.

CONCLUSIONS: Both pooled and meta-analyses of data from the ASCEND and CAPACITY trials consistently favored pirfenidone in reducing the risk of ACM in patients with IPF over time. These findings highlight the robustness of pooled data analyses in evaluating drug efficacy outcomes in the pirfenidone phase 3 trials.

KARINA RAIMUNDO, BPHARM, MS / SENIOR HEALTH ECONOMIST, US MEDICAL AFFAIRS /

GENENTECH, INC. / SOUTH SAN FRANCISCO, CALIFORNIA, UNITED STATES

Application Title: In-hospital length of stay and mortality for patients with idiopathic pulmonary fibrosis (IPF) in the US

AUTHORS: Karina Raimundo; Eunice Chang; Michael Broder; James L. Zazzali

GENERAL AUDIENCE SUMMARY

OBJECTIVE: To describe demographic characteristics, length of stay, and in-hospital mortality of patients hospitalized with IPF.

METHODS: We used data from the Nationwide Inpatient Sample (NIS), from 2009-2011 for this retrospective cohort study. Patients were included if they had at least one inpatient claim with IPF as primary or secondary discharging diagnosis (ICD-9-CM code 516.3, 516.31) in the calendar year. Descriptive analyses are reported for hospitalizations in 2011 (findings were similar in 2009-2010). We report data for all IPF hospitalizations, and IPF as the primary code (IPF-P). All variables were weighted to represent national estimates.

RESULTS: In 2011, we identified 16,477 IPF hospitalization claims. 50.9% of those were of male patients, average 71.1 years. Medicare was the primary payer for most hospitalizations (77.4%). Patients had a high number of chronic conditions (mean: 4.6), with 47.9% having cardiovascular comorbid conditions, most commonly ischemic heart disease (30.7%) and congestive heart failure (30.0%). Of all hospitalizations, 26% were for IPF-P. About half (50.3%) of IPF-P hospitalizations had evidence of preceding emergency room (ER) services. In-hospital death occurred in 14.5% of IPF-P (vs. 10.3% in all hospitalizations). Mean length of stay for patients who died in the hospital was longer (10.6 days) than for all hospitalizations (7.6 days). Among patients who died during their hospitalization, IPF-P patients had an even longer length of stay (11.5 days) than non-IPF-P (10.2 days).

CONCLUSIONS: As expected given the overall IPF population, IPF patients who are hospitalized are older and have many comorbid conditions. Half the hospitalizations had evidence of ER services. Patients who die during hospitalization have, on average, longer length of stay. Patients with IPF-P had even longer lengths of stay than non-IPF-P. Admissions of patients with IPF can be linked to in-hospital mortality, particularly if IPF is the primary reason for admission. Further investigation into predictors of mortality may allow at-risk patients to be identified and their care modified.

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KARINA RAIMUNDO, BPHARM, MS / SENIOR HEALTH ECONOMIST, US MEDICAL AFFAIRS / GENENTECH, INC. / SOUTH SAN FRANCISCO, CALIFORNIA, UNITED STATES

Clinical and economic burden of idiopathic pulmonary fibrosis

AUTHORS: Karina Raimundo; Eunice Chang; Michael Broder; Gillis Carrigan; James L. Zazzali; Jeffrey J. Swigris

GENERAL AUDIENCE SUMMARY

OBJECTIVE: Idiopathic pulmonary fibrosis (IPF) is a severe respiratory disease of unknown cause and poor prognosis, and with limited treatment options. Our goal is to describe the prevalence, and economic and health care burden of IPF.

METHODS: Retrospective cohort study using a HIPAA-compliant de-identified commercial healthcare claims database from 2009-2011. Inclusion criteria per study year (patients may be included in multiple years): 1+ inpatient claim or 2+ outpatient claims with IPF diagnosis code (ICD-9: 516.3); continuously enrolled with health plan and no other type of interstitial lung disease after their last IPF claim. We described one-year prevalence estimates per year (2009–2011). Descriptive analyses of all-cause, respiratory-related healthcare resource utilization and costs are presented (2011). All costs were inflated to 2011 US dollars.

RESULTS: Overall prevalence of IPF was 28.8, 28.1 and 19.8 per 100,000 persons in 2009, 2010 and 2011 and increased substantially with age (table). In 2011, 1,136 patients met inclusion criteria (mean age: 71.3 years [SD: 10.6], 49.1% female, mean number of chronic conditions: 5.9, Charlson Comorbidity Index (CCI): 3.2). Those patients had, on average, 18.5 office visits, 38% had at least one hospitalization visit and 31% had at least one emergency room (ER) visit for any cause. Mean all-cause total healthcare costs were $61,671 per patient; non-medication costs accounted for 88.8% of the total healthcare costs. Patients had 5.7 respiratory-related office visits; 19.8% were hospitalized at least once; and 14.3% went to the ER. Mean total respiratory-related healthcare costs were $21,762 and non-medication costs accounted for $19,604. Similar patterns were observed in 2009 and 2010 (figure).

CONCLUSION: Idiopathic pulmonary fibrosis is a chronic severe condition with higher prevalence in elderly patients. Patients with IPF have high comorbidity rates and are intense users of healthcare resources, leading to a high total economic healthcare burden. This analysis may have underestimated the total burden of IPF since patients may have received their diagnosis at any time in the study year.

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169
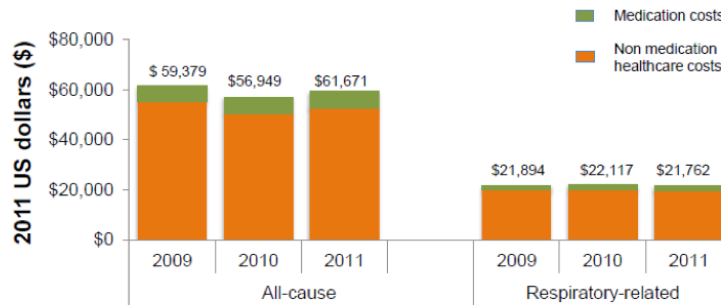
*All costs were inflated to 2011 US dollars

	2009	2010	2011
	Overall		
	28.8	28.1	19.8
	By age group		
≤11	0.2	0.4	0
12-24	0	0.3	0.1
25-44	3.3	3.4	1.9
45-64	22.2	22.8	13.9
65-74	99	74.8	62.7
75-79	161.1	124.1	100.5
80+	185.5	179.4	165.9

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session notes

session notes

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session notes

session notes

session notes

session notes

session notes

acronym glossary

6MWD: six minute walk distance test

A

ABG: arterial blood gas

ACCP: American College of Chest Physicians

ADLs: activities of daily living

AIP: acute interstitial pneumonia

ALAT: Asociacion Latinoamericana de Torax

ARDS: acute respiratory distress syndrome

ATS: American Thoracic Society

B

BAL: bronchoalveolar lavage

BiPAP: bi-level positive airway pressure

BP: blood pressure

BX: biopsy

C

CDC: Centers of Disease Control and Prevention

CF: cystic fibrosis

CHF: congestive heart failure

CLD: chronic lung disease

CMS: Center for Medicare and Medicaid Services

CO: carbon monoxide

CO_2: carbon dioxide

COP: cryptogenic organizing pneumonia

COPD: chronic obstructive pulmonary disease

CPAP: continuous positive airway pressure

CPR: cardiopulmonary resuscitation

CRT: Certified Respiratory Therapist

CT: CAT scan or computerized axial tomography

CTD-ILD: connective tissue associated interstitial lung disease

CXR: chest X-ray

D

DIP: desquamative interstitial pneumonia

DLCO: diffusing capacity of carbon monoxide

DNR: do not resuscitate

DOE: dyspnea on exertion

DPAP: demand positive airway pressure

DPLD: diffuse parenchymal lung disease

DX: diagnosis

E

ECG or EKG: electrocardiogram

ECHO: echocardiogram

EMA: European Medicines Agency

ERS: European Respiratory Society

ERV: expiratory reserve volume

ET: endotracheal tube

F

FDA: Food and Drug Administration

FEF: forced expiratory flow

FEFMAX: forced expiratory flow at maximum effort

FEV: forced expiratory volume

FEV1: forced expiratory volume in 1 second

FIP: familial interstitial pneumonia

FPF: familial pulmonary fibrosis

FRC: functional residual capacity

FVC: forced vital capacity

G

GERD: gastroesophageal reflux disease

GI: gastrointestinal

GP: general practitioner

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 O_2 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 pneumonitis

O

O_2: oxygen

OAD: obstructive airway disease

OLD: occupational lung disease

OSA: obstructive sleep apnea

OTC: over the counter

P

PaO_2: partial pressure of oxygen in arterial blood

PAP: positive airway pressure

PCO_2: 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 fest

PH: pulmonary hypertension

PLB: pursed lip breathing

PND: paroxysmal nocturnal dyspnea/post nasal drip

PO_2: 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

SaO$_2$: arterial blood oxygen saturation

SOB: shortness of breath

SSDI: Social Security Disability Insurance

SSI: Supplemental Security Insurance

T

TLC: total lung capacity

TTO$_2$: 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

VCO$_2$: carbon dioxide production

VO$_2$: oxygen consumption

VQ SCAN: ventilation perfusion scan

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