
# Ganesh Raghu, MD, FCCP, FACP

Professor of Medicine & Lab Medicine (Adjunct) ;  University of Washington(UW)

***DIRECTOR : The CENTER for INTERSTITIAL  LUNG  DISEASES***

***Co-Director:  Scleroderma Clinic***

UW Medical center Seattle, WA  98195

# Ganesh Raghu, MD

## Disclosures

Consultant : Boehringer-Ingelheim, Biogen , BMS, Celgene, Centocor (Johnson&Johnson/Janssen), Fibrogen ,Gilead Sciences, Medimmune, Promedior, Roche-Genentech, Sanofi-Aventis, UCB, Veracyte

Research grant : National Institutes of Health(NIH), Bethesda, MD,USA

(clinical research network; IPFnet)

-Idiopathic pulmonary fibrosis studies

Pulmonologist/Consultant : *longstanding interest and expertise in Interstitial lung diseases(ILD)/sarcoidosis/pulmonary fibrosis*; *dedicated to field of ILD, patient advocate*

# Idiopathic pulmonary fibrosis(IPF)

- The new Era of IPF :  2017 –

- *New perspectives in IPF therapy: hopes and questions*

AMERICAN THORACIC SOCIETY DOCUMENTS

# An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis

## An Update of the 2011 Clinical Practice Guideline

Ganesh Raghu, Bram Rochwerg, Yuan Zhang, Carlos A. Cuello Garcia, Arata Azuma, Juergen Behr, Jan L. Brozek, Harold R. Collard, William Cunningham*, Sakae Homma, Takeshi Johkoh, Fernando J. Martinez, Jeffrey Myers, Shandra L. Protzko, Luca Richeldi, David Rind, Moisés Selman, Arthur Theodore, Athol U. Wells, Henk Hoogsteden, and Holger J. Schünemann; on behalf of the ATS, ERS, JRS, and ALAT

*This guideline is dedicated to the memory of Mr. William Cunningham (June 7, 1935–October 23, 2014)*

THIS OFFICIAL CLINICAL PRACTICE GUIDELINE OF THE AMERICAN THORACIC SOCIETY (ATS) WAS APPROVED BY THE ATS, MAY 2015, THE EUROPEAN RESPIRATORY SOCIETY (ERS), APRIL 2015, THE JAPANESE RESPIRATORY SOCIETY (JRS), APRIL 2015, AND THE LATIN AMERICAN THORACIC ASSOCIATION (ALAT), APRIL 2015

**AJRCCM 2015; 192:238-48**

**Background:** This document updates the American Thoracic Society/European Respiratory Society/ Japanese Respiratory Society/Latin American Thoracic Association guideline on idiopathic pulmonary fibrosis

applied, and recommendations were formulated, written, and graded exclusively by the nonconflicted panelists.

**Results:** After considering the confidence in effect estimates, the

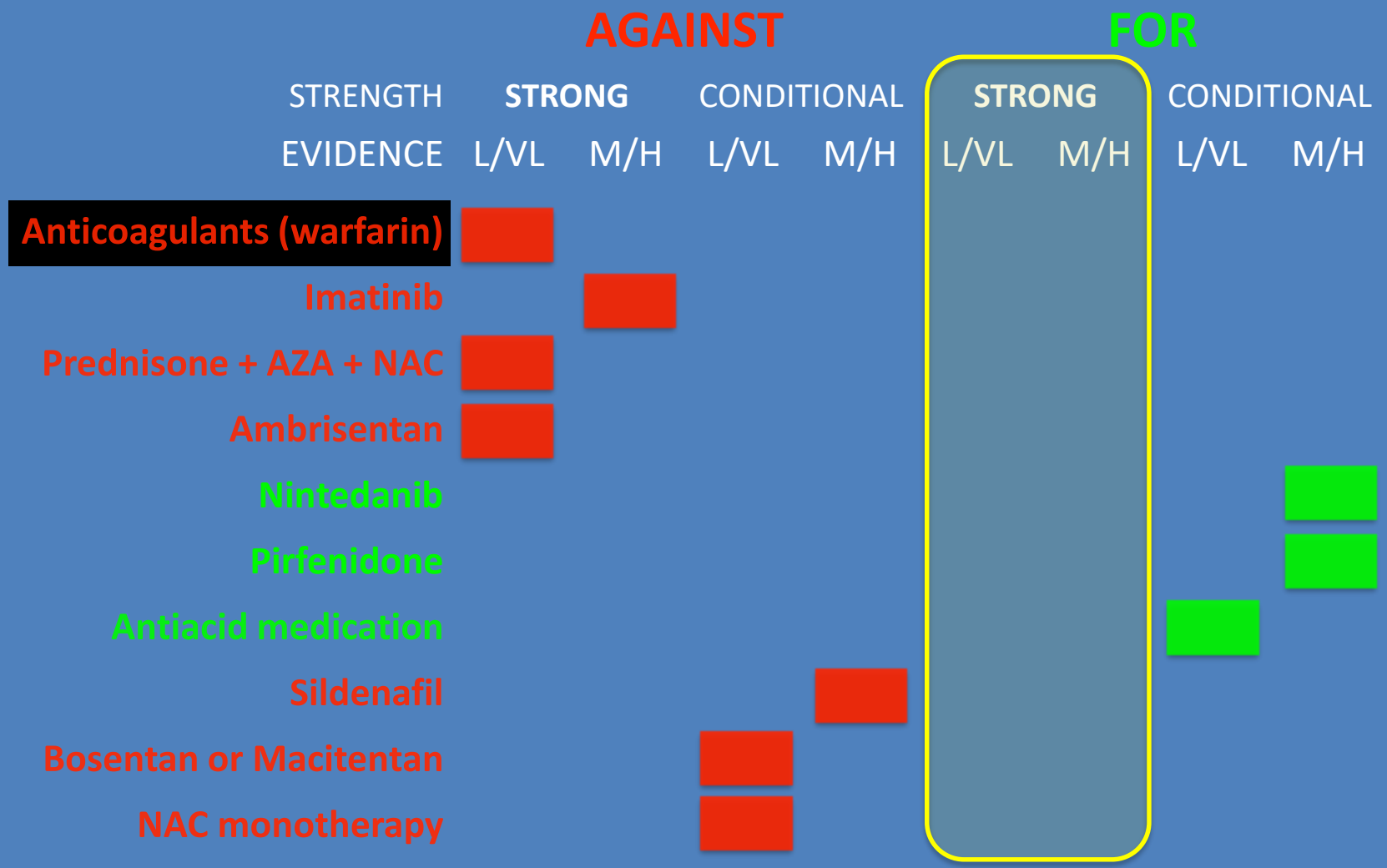
# IPF Treatment guidelines –evidence based, update

## Raghu et al AJRCCM 2015; 192:238-48

| | AGAINST | | | | FOR | | | |
|---|---|---|---|---|---|---|---|---|
| STRENGTH | **STRONG** | | CONDITIONAL | | **STRONG** | | CONDITIONAL | |
| EVIDENCE | L/VL | M/H | L/VL | M/H | L/VL | M/H | L/VL | M/H |
| **Anticoagulants (warfarin)** | | | | | | | | |
| **Imatinib** | | | | | | | | |
| **Prednisone + AZA + NAC** | | | | | | | | |
| **Ambrisentan** | | | | | | | | |
| **Nintedanib** | | | | | | | | |
| **Pirfenidone** | | | | | | | | |
| **Antiacid medication** | | | | | | | | |
| **Sildenafil** | | | | | | | | |
| **Bosentan or Macitentan** | | | | | | | | |
| **NAC monotherapy** | | | | | | | | |

# IPF Treatment guidelines –evidence based, update

**Raghu et al AJRCCM 2015; 192:238-48**



# Nintedanib and Pirfenidone

## New Antifibrotic Treatments Indicated for Idiopathic Pulmonary Fibrosis Offer Hopes and Raises Questions

Ever since Louis Hamman and Arnold Rich described the first fatal case of pulmonary fibrosis of unknown etiology more than 80 years ago, the medical community has been challenged by the lack of effective pharmacologic therapy (1). In 2000, a panel of experts proposed idiopathic pulmonary fibrosis (IPF) as a distinct lethal entity in adults (2). In 2011, more precise diagnostic criteria were described (3). For decades, patients with IPF were treated with varying doses/duration of corticosteroids and, subsequently, with the combination of prednisone plus azathioprine or cyclophosphamide. More recently, *N*-acetylcysteine, combined with prednisone and azathioprine, was



**Raghu and Selman , AJRCCM, Feb 1 2015**

# Idiopathic Pulmonary Fibrosis

## Treatment with Pirfenidone and Nintedanib: 2015 -Raghu and Selman AJRCCM ;Feb 2015

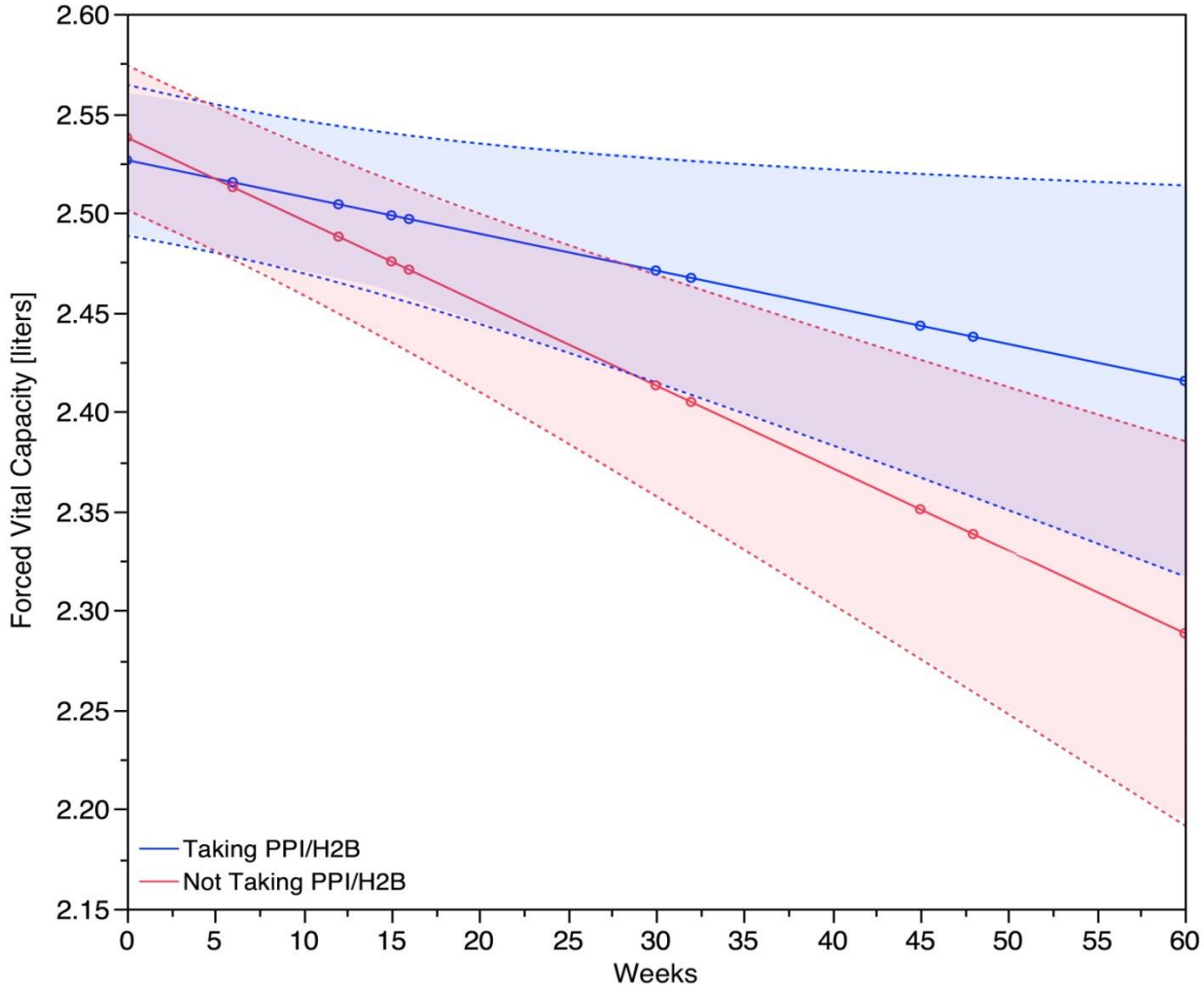
- ***Approval for treatment for IPF (FDA and EMA)*** "**Blanket treatment**" ( regardless of status of disease and/or comorbid conditions)
- ***Results of phase 3 clinical trials in a precise subgroup of patients with IPF***
- ***Decline in FVC decline over 1 yr***
- ***without symptomatic relief***
- ***Significant side effects ( GI in both ;rash with pirfenidone)***
- ***Tolerated by patients in the context of clinical trials***

# IPF : Treatment with Pirfenidone and Nintedanib: 2015
## -Raghu and Selman AJRCCM ;Feb 2015

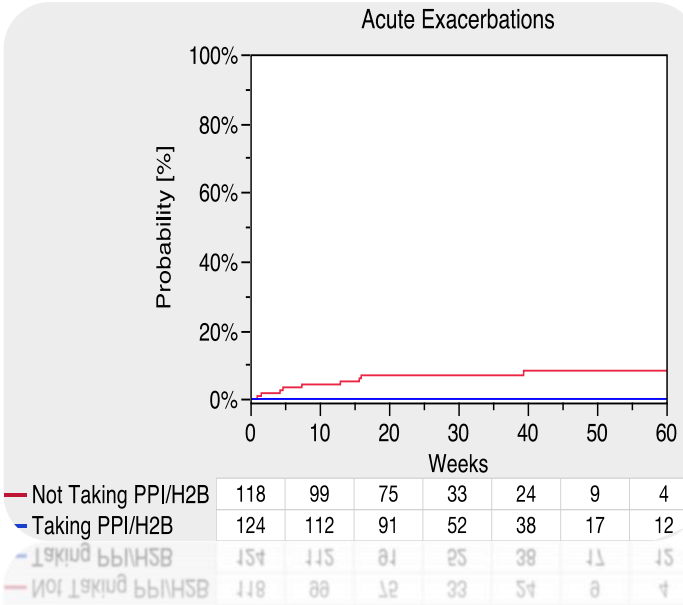
- ***Unkown effects :***
- whether the lower rate of decline in FVC in patients lasts beyond 1 yr in patients with mild –moderate impairment(PFTs)
- applicable to the entire spectrum of patients with IPF, especially those with severe functional impairment and/or known comorbidities.
- Long term effects and if tolerated in patients in “real world”
- ***Is one better than the other?: No head-to-head comparison***
- ***if used sequential or in combination with both or with other drugs***
- ***Cost effective-benefit-ratio***
- ***Case –by Case basis***

# Anti-acid treatment and disease progression in idiopathic pulmonary fibrosis: an analysis of data from three randomised controlled trials

*Joyce S Lee, Harold R Collard, Kevin J Anstrom, Fernando J Martinez, Imre Noth, Rhonda S Roberts, Eric Yow, Ganesh Raghu, for the IPFnet Investigators**




The Lancet-RM July 2013



# Antacid therapy and disease outcomes in idiopathic pulmonary fibrosis: a pooled analysis

Michael Kreuter, Wim Wuyts, Elisabetta Renzoni, Dirk Koschel, Toby M Maher, Martin Kolb, Derek Weycker, Paolo Spagnolo, Klaus-Uwe Kirchgaessler, Felix J F Herth, Ulrich Costabel

## Summary

**Background** Gastro-oesophageal reflux disease is a potential risk factor for the development and progression of idiopathic pulmonary fibrosis (IPF). We aimed to investigate the effect of antacid therapy on disease progression in

*Lancet Respir Med* 2016; 4: 381–89

**Interpretation** Antacid therapy did not improve outcomes in patients with IPF and might potentially be associated with an increased risk of infection in those with advanced disease.

Eur Respir J 2005; 26: 755–758
DOI: 10.1183/09031936.05.00104105


**EDITORIAL**

# Clinical trials in idiopathic pulmonary fibrosis: a word of caution concerning choice of outcome measures

**W.C. Johnson* and G. Raghu#**

**Ganesh Raghu, The Lancet Resp Med ,Sept 1 2016 e48**
www.thelancet.com/respiratory **Vol 4**



## Anti-acid treatment in patients with IPF: interpret results from post-hoc, subgroup, and exploratory analyses with great caution

controlled. Seventh, there were many other unknowns: whether patients were taking the anti-acid treatment on a daily or as needed basis for symptomatic GER or simply taking the medication for assumed silent GER or for IPF; whether patients were taking the same dose and the same anti-acids captured in case report and during the pH monitoring.[3] It is conceivable that the increased frequency of apparent respiratory infections (even if the infections are assumed to be confirmed based on prespecifications) in the subgroup of patients with FVC less than 70% predicted at baseline (that was defined post hoc) could have been

The results from all the post-hoc, subgroup, and exploratory analyses must be interpreted with great caution and the data generated from such analyses must always be considered at best as hypothesis-generating.[4] In fact,

Johnson WC, Raghu G. Clinical trials in idiopathic pulmonary fibrosis: a word of caution concerning choice of outcome measures. Eur Respir J 2005; 26: 755–58.

# Anti-acid treatment in patients with IPF: interpret results from post-hoc, subgroup, and exploratory analyses with great caution

**Ganesh Raghu: www.thelancet.com/resp**

**Vol 4 The Lancet Resp Med ,Sept 1 2016 e48**

Kreuter M, Wuyts W, Renzoni E, et al. Anti-acid therapy and disease outcomes in idiopathic pulmonary fibrosis: a pooled analysis. Lancet Respir Med 2016; 4: 381–89.

- Kreuter study : major concerns

-the pooled population of patients with IPF enrolled in the pirfenidone trials; analyses based on data noted in case report forms that was not intended to capture data for the diagnosis of GERD or the specifics of anti-acid treatment at baseline or during study period.

- not designed to determine the frequency of infection; there were no pre specified criteria that defined infection or respiratory infection, nor were the presumed episodes of infection adjudicated
- the respiratory infections proposed to be associated with anti-acid treatment were noted in exploratory analyses only in the subgroup of patients with a predicted forced vital capacity (FVC) of less than 70%, an analysis which was defined post hoc.
- the rates of all-cause hospital admission, gastrointestinal adverse effects, and respiratory infections were similar in the groups of patients who received and did not receive anti-acid therapy

# Anti-acid treatment in patients with IPF: interpret results from post-hoc, subgroup, and exploratory analyses with great caution

**Ganesh Raghu: www.thelancet.com/resp**

**Vol 4 The Lancet Resp Med ,Sept 1 2016 e48**

Kreuter M, Wuyts W, Renzoni E, et al. Anti-acid therapy and disease outcomes in idiopathic pulmonary fibrosis: a pooled analysis. Lancet Respir Med 2016; 4: 381–89.

- Kreuter study : major concerns/hypothesis generating
- it is conceivable that the increased frequency of apparent respiratory infections *(even if the infections are assumed to be confirmed based on pre specifications)* in the subgroup of patients with FVC less than 70%predicted at baseline *(that was defined post hoc)* could have been due to the abnormal GER, or altered lung microbiome, independent of the anti-acid treatment.
- **subgroup of patients with advanced IPF and the alleged increased infection might therefore have been due to abnormal GER and micro aspiration and not due to the anti-acid treatment per se**

Anti-acid treatment in patients with IPF: interpret results from post-hoc, subgroup, and exploratory analyses with great caution

**Ganesh Raghu: www.thelancet.com/resp**

**Vol 4 The Lancet Resp Med ,Sept 1 2016 e48**

Kreuter M, Wuyts W, Renzoni E, et al. Anti-acid therapy and disease outcomes in idiopathic pulmonary fibrosis: a pooled analysis. Lancet Respir Med 2016; 4: 381–89.

- Kreuter study : major concerns (contd)
- the gastrointestinal adverse effects were similar irrespective of anti-acid therapy use, even when patients were stratified post hoc by baseline FVC.
- patients were presumed to have abnormal gastro-esophageal reflux (GER); the intensity, frequency, and extent of abnormal GER are unknown
- the dose, duration, and specific anti-acid treatment (eg, specific H2 receptor antagonists, proton pump inhibitors [PPIs], buffers such as magnesium, calcium, or both) taken throughout the study period is unknown or not controlled.
- many other unknowns: anti-acid treatment on a daily or as needed basis for symptomatic GER or simply taking the medication for assumed silent GER or for IPF ? same dose and the same anti-acids captured in case report forms at baseline and throughout the trial period ? adhering to conservative measures to decrease the risks for aspiration?

# Antacid therapy and disease outcomes in idiopathic pulmonary fibrosis: a pooled analysis

Michael Kreuter, Wim Wuyts, Elisabetta Renzoni, Dirk Koschel, Toby M Maher, Martin Kolb, Derek Weycker, Paolo Spagnolo, Klaus-Uwe Kirchgaessler, Felix J F Herth, Ulrich Costabel

**Summary**

**Background** Gastro-oesophageal reflux disease is a potential risk factor for the development and progression of idiopathic pulmonary fibrosis (IPF). We aimed to investigate the effect of antacid therapy on disease progression in

*Lancet Respir Med* 2016; 4: 381–89

- **Correspondence**
- www.thelancet.com/respiratory **Vol 4 September 2016 e48**

## Authors' reply

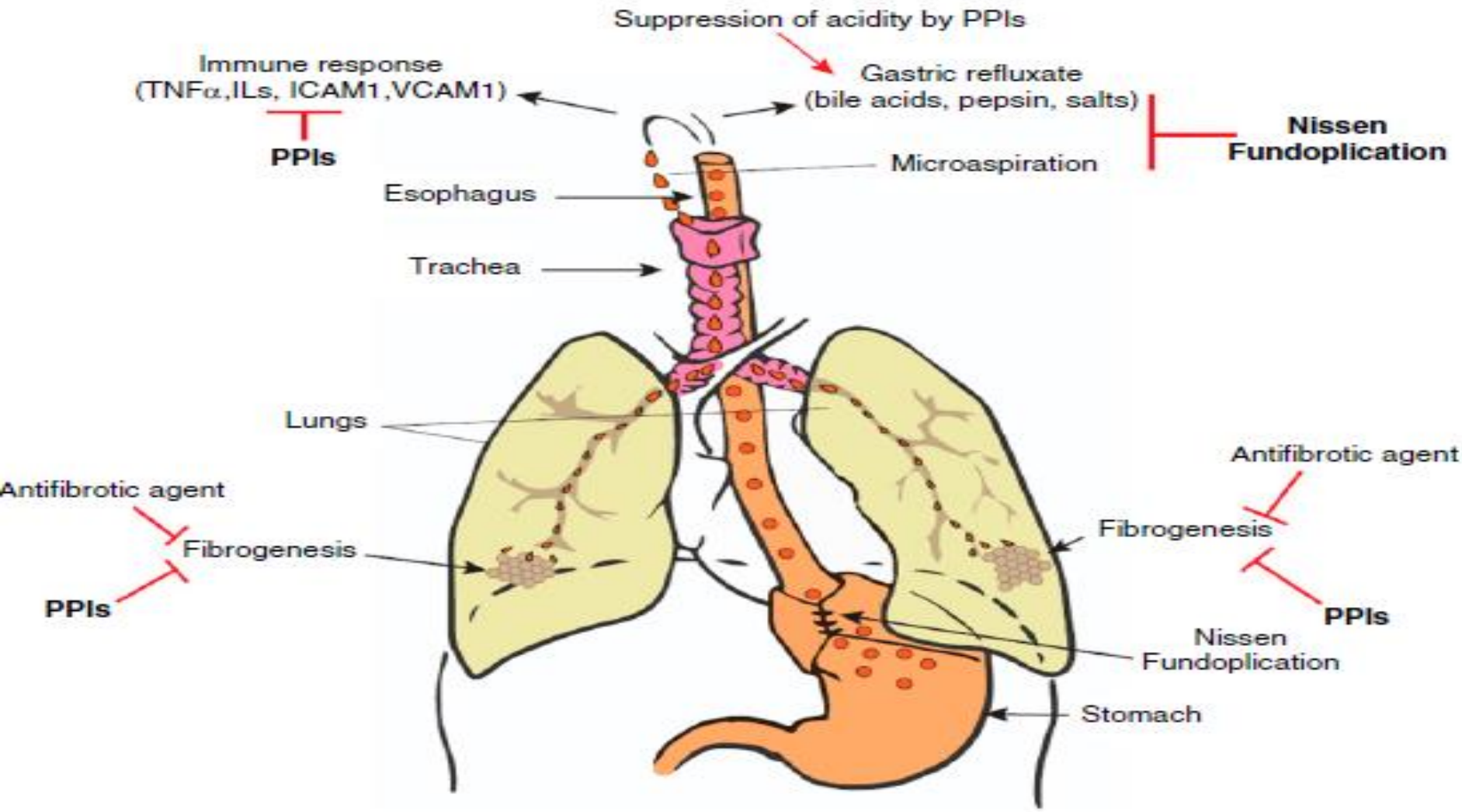
We thank Ganesh Raghu for his kind interest in our Article.[1] Currently, the role of antacid treatment as a therapy for idiopathic pulmonary fibrosis is unclear due to missing prospective data, conflicting results from retrospective and post-hoc analyses as well as preclinical data suggesting possible anti-inflammatory and antifibrotic properties of proton pump inhibitors.[2–5] We agree with Raghu regarding the limitations

In conclusion, we completely agree with Raghu, that prospective randomised, double-blind placebo controlled studies assessing the role of antacid therapy in idiopathic pulmonary fibrosis are urgently needed and we look forward to collaborating with him in this regard. Until these trials are completed neither the efficacy nor the safety of proton pump inhibitors in idiopathic pulmonary fibrosis can be assumed.

Ghebre and Raghu AJRCCM 2016

# Idiopathic Pulmonary Fibrosis: Novel Concepts of Proton Pump Inhibitors as Antifibrotic Drugs

Yohannes T. Ghebre[1] and Ganesh Raghu[2]



# Idiopathic Pulmonary Fibrosis: Increased Survival with "Gastroesophageal Reflux Therapy" Fact or Fallacy?

Ganesh Raghu, M.D.

**Raghu G: Am. J. Respir. Crit. Care Med. 2011; 184: 1330-1332.**

*Only prospective, randomized clinical trial will provide the high quality evidence –and needed to answer this important question*

# Laparoscopic anti-reflux surgery for idiopathic pulmonary fibrosis at a single centre

Ganesh Raghu[1], Ellen Morrow[2], Bridget F. Collins[1], Lawrence A.T. Ho[1], Marcelo W. Hinojosa[2], Jennifer M. Hayes[1], Carolyn A. Spada[1], Brant Oelschlager[2], Chenxiang Li[3], Eric Yow[3], Kevin J. Anstrom[3], Dylan Mart[2], Keliang Xiao[2] and Carlos A. Pellegrini[2]

27 patients with progressive IPF underwent LARS. At time of surgery, the mean age was 65 years and mean FVC was 71.7% pred. Using a regression model, the estimated benefit of surgery in FVC % pred over 1 year was 5.7% (95% CI −0.9–12.2%, p=0.088) with estimated benefit in FVC of 0.22 L (95% CI −0.06–0.49 L, p=0.12). Mean DeMeester scores decreased from 42 to 4 (p<0.01). There were no deaths in the 90 days following surgery and 81.5% of participants were alive 2 years after surgery.

Patients with IPF tolerated the LARS well. There were no statistically significant differences in rates of FVC decline pre- and post-LARS over 1 year; a possible trend toward stabilisation in observed FVC warrants prospective studies. The ongoing prospective randomised controlled trial will hopefully provide further insights regarding the safety and potential efficacy of LARS in IPF.

# WRAP-IPF

Randomized clinical trial

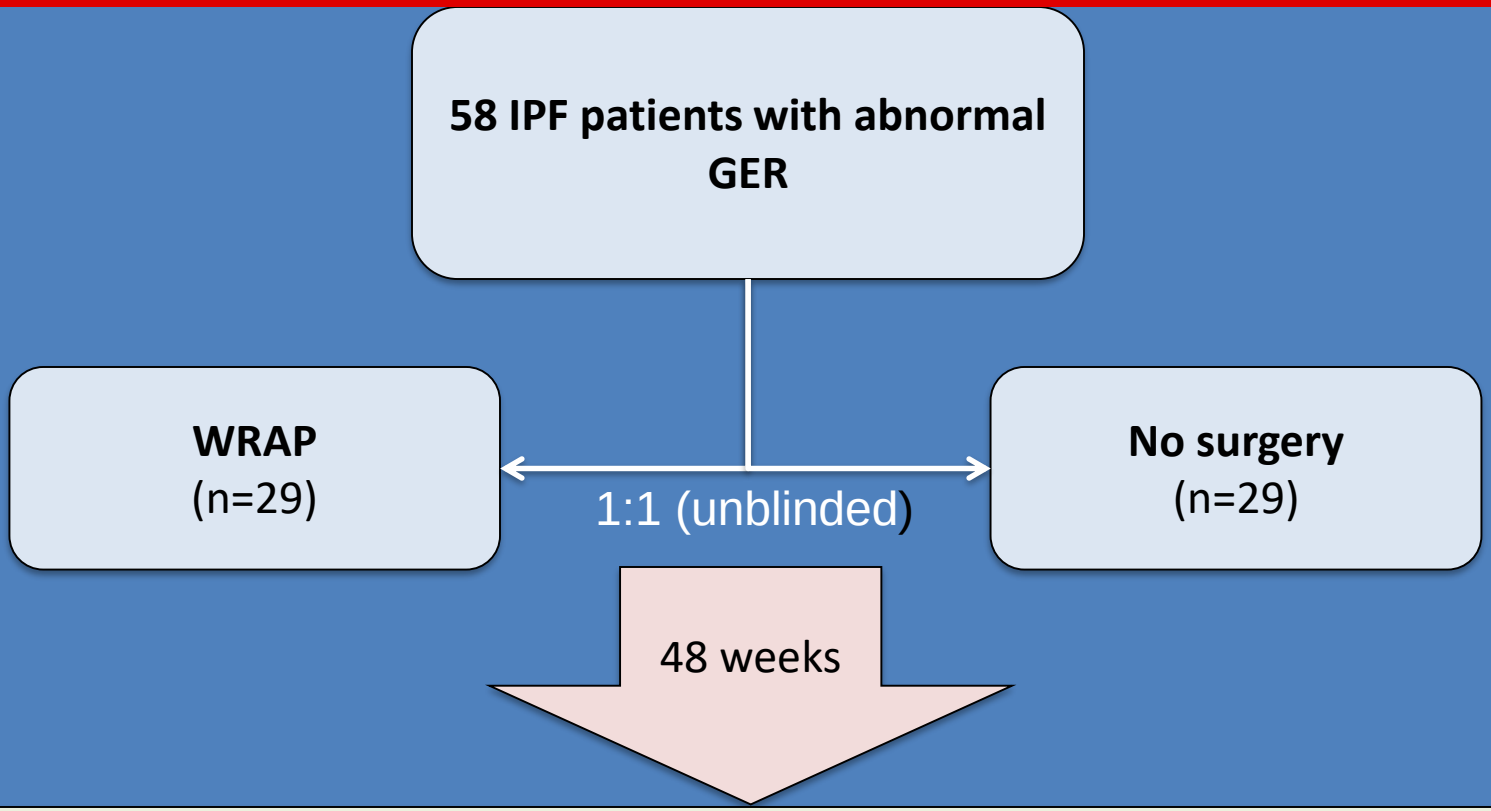
NIH sponsored phase 2 clinical trial

# WRAP-IPF

- W eighing Risks and benefits of Laparoscopic Anti-Reflux Surgery in Patients with Idiopathic Pulmonary Fibrosis (WRAP-IPF):

- **A Phase II Clinical Trial**

# WRAP-IPF : Study design

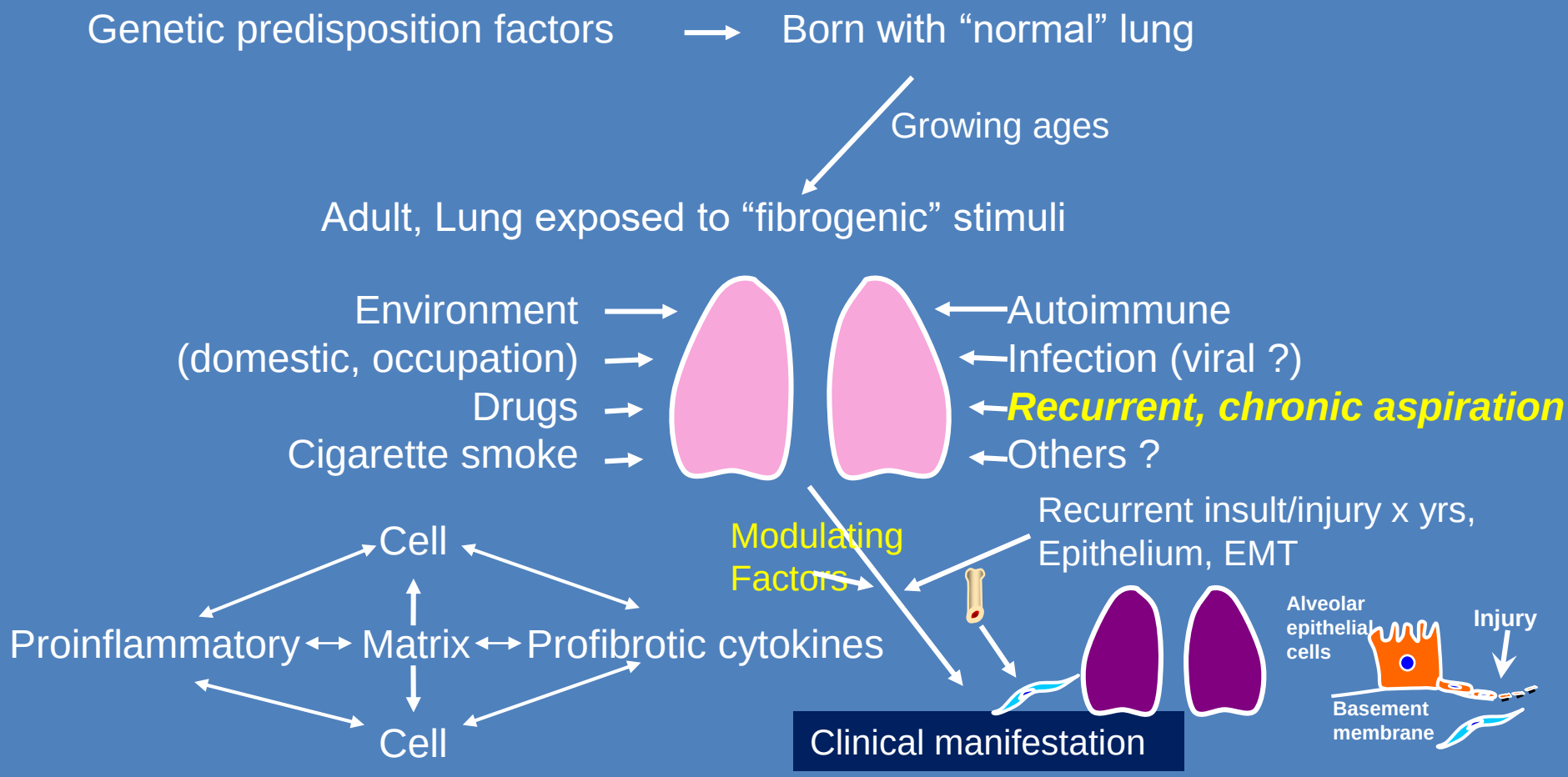



**Primary endpoint: Change in FVC**

Secondary endpoints (selected): Disease progression, categorical FVC change, acute exacerbation, non-elective hospitalization, mortality

# Pulmonary Fibrosis of Unknown Etiology

## Conceptual Pathogenesis of Usual Interstitial Pneumonia (UIP)



# Current Paradigm of IPF Pathogenesis

Exogenous and Endogenous stimuli

Dust ,Fumes,
Cigarette smoke
**GER/Microaspiration**
Autoimmune conditions

Drugs
Infections-viruses
Radiation
Other diseases

Microscopic lung injury:
Separated spatially and temporally

Intact | Wound healing | Aberrant

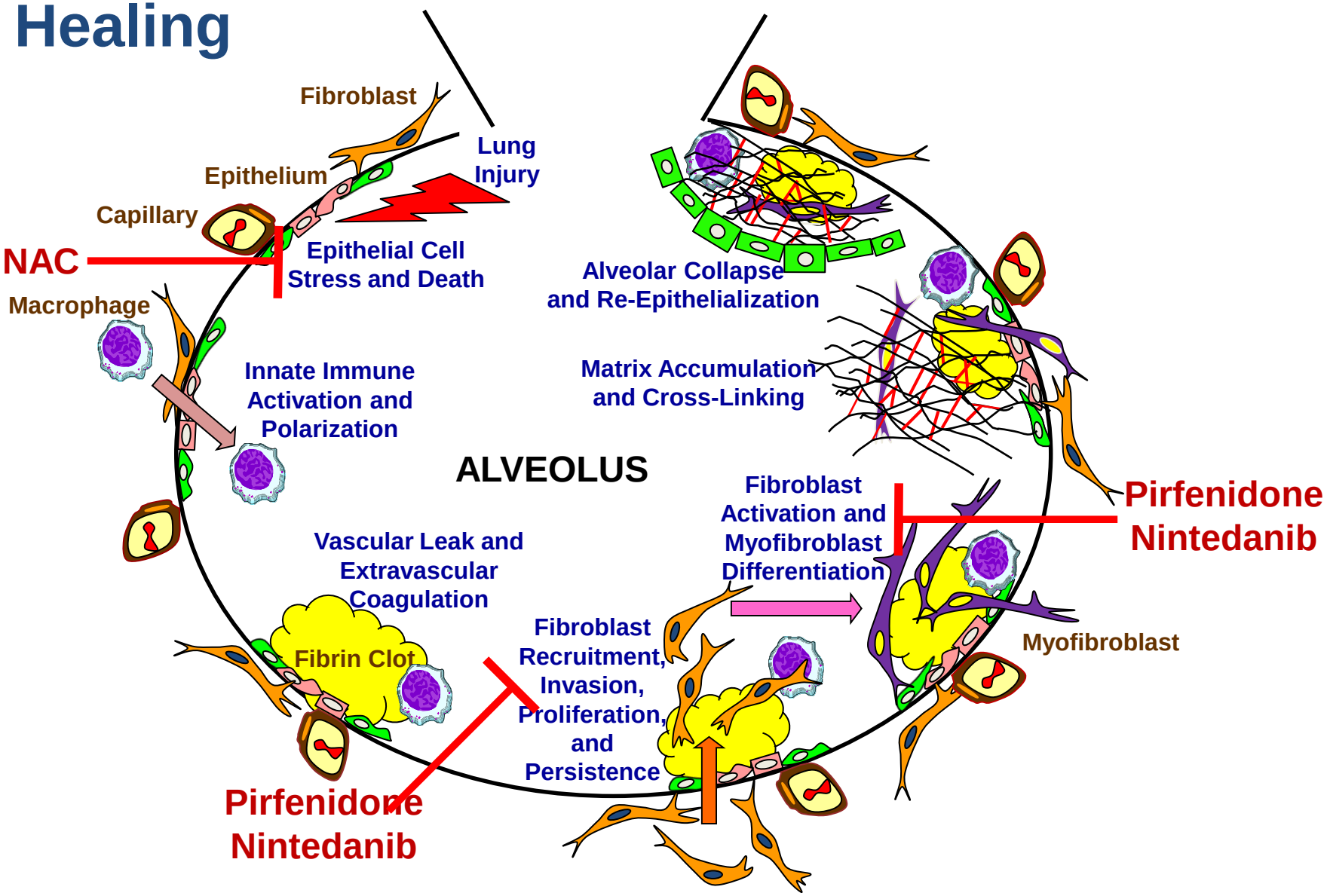
**Genetic predisposition**

Lung homeostasis

Idiopathic Pulmonary Fibrosis

Steele MP, Schwartz DA. *Annu Rev Med.* 2013;64:265-276.
Selman M, King TE, Pardo A, *Ann Intern Med* 2001

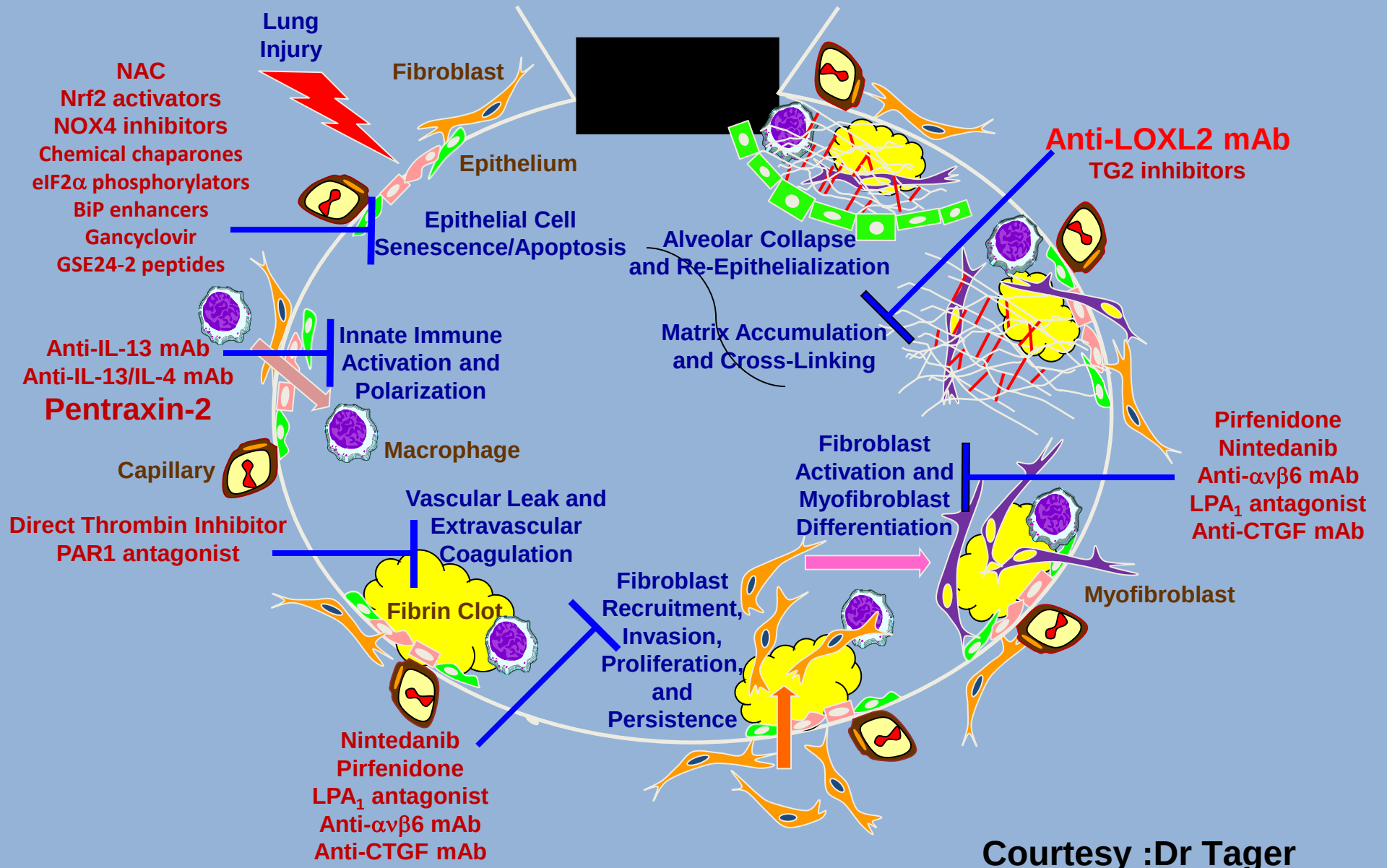
# Fibrosis as Chronic Injury and Aberrant Wound Healing




Ahluwalia N, Shea BS, Tager AM, *AJRCCM* 2014

# Novel Targets For The Future: What's Promising?

## A LOT!!! www.clinicaltrials.gov




Courtesy :Dr Tager

# Progression-free survival in patients with idiopathic pulmonary fibrosis given simtuzumab versus placebo: a randomised, double-blind, controlled, phase 2 trial

Raghu et al Lancet-RM
Jan 2017

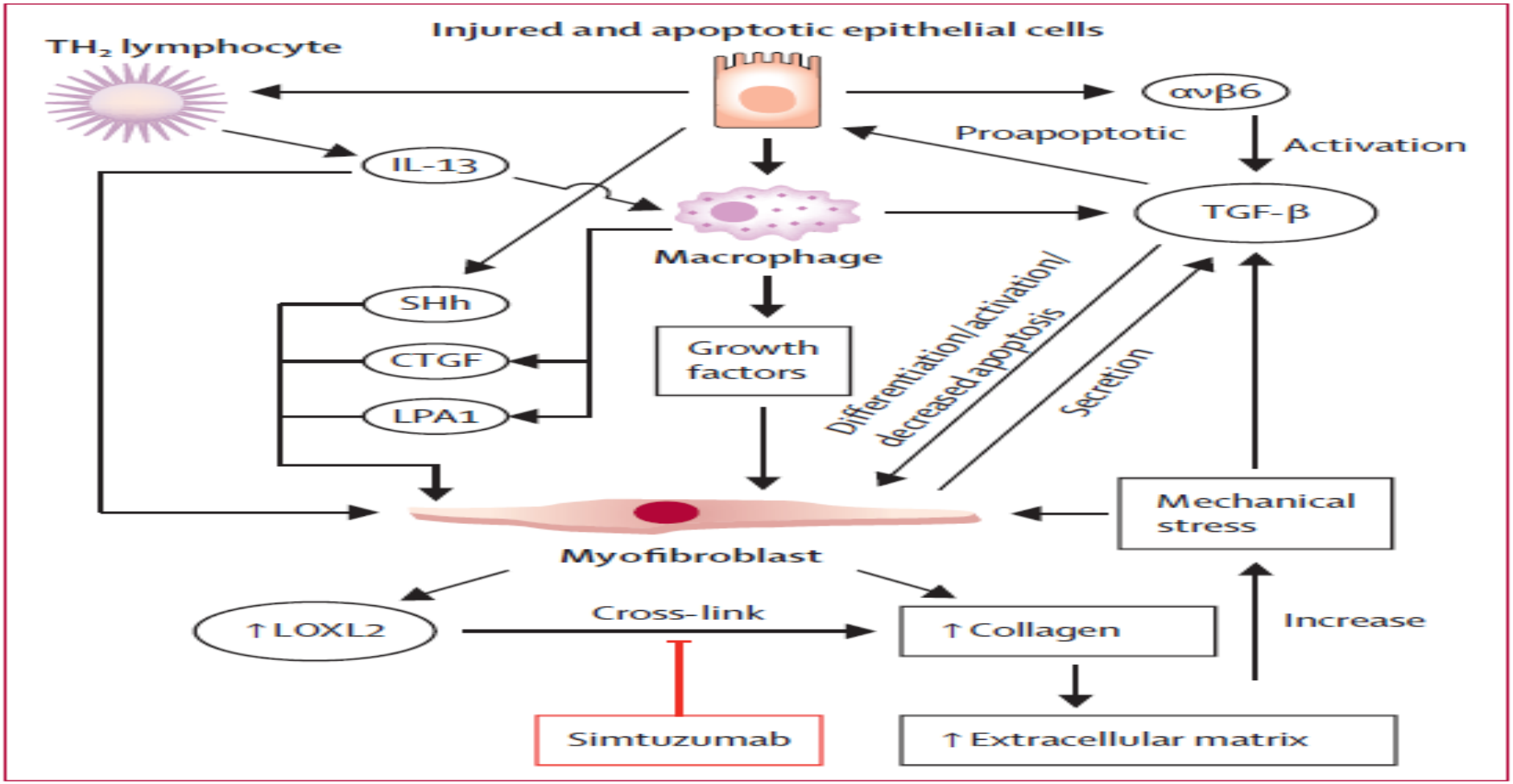



***Figure 1:*** **Factors involved in the pathogenesis of IPF**
αvβ6=α-v-β-6 integrin. CTGF=connective tissue growth factor. IL-13=interleukin-13. LOXL2=lysyl-oxidase-like 2. LPA1=lysophosphatidic acid receptor 1. SHh=sonic hedgehog. TGF-β=transforming growth factor-β. $TH_2$=type 2 T helper cell.

# Simtuzumab(SIM) in Idiopathic Pulmonary Fibrosis: Results of a Randomized Clinical Trial*

## Conclusions

- **Treatment of IPF with SIM did not demonstrate efficacy as measured by:**
  - PFS or overall survival in ITT population or patients with elevated sLOXL2 at baseline
  - Prespecified secondary endpoints (change in FVC, DLCO, 6MWD, or SGRQ) in ITT population or subgroup with elevated LOXL2
  - Rates of hospitalization
- There does not appear to be a positive or negative treatment interaction between SIM and pirfenidone
- No significant difference in pattern of AEs observed in SIM- and placebo-treated groups

***Raghu et al Lancet Resp Medicine; Jan 2017 .**

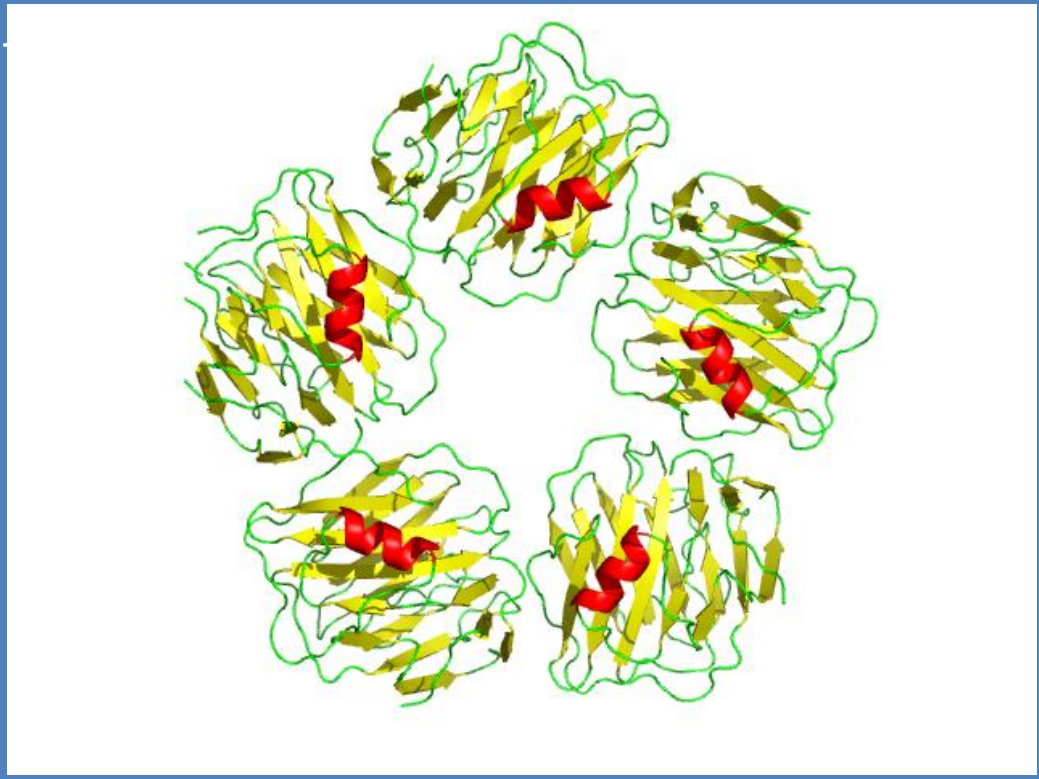
# IPF- some, ongoing /initiated clinical trials clinical trial.gov

- Serum Amyloid P/Pentraxin-2( PROMOTE Trial; Promedior)
- IL4/IL13 ( ESTAIR Trial, SANOFI)
- CTGF(PRAISE  Trial; Fibrogen )

- WRAP –IPF- anti GER concept ( NIH, USA)
- CLEAN UP-IPF –antimicrobial concept ( NIH ,USA)

# Pentraxin-2 (PTX-2)

- PTX-2 (Serum Amyloid P [SAP]), a member of the pentraxin family of proteins, is a 125 kD circulating plasma protein
  - Synthesized by the liver
  - Homopentamer: 5 x 25 kD monomers
- Acts as a pattern recognition receptor for the innate immune system.
- Inhibits the differentiation of monocytes into fibrocytes
- Shown to stop/reverse fibrosis in multiple organ systems
- Recombinant human PTX-2 produced in CHO cells = PRM-151



J Lu, LL. Marnell, KD. Marjon, C Mold, TW. Du Clos & PD. Sun. *Nature* **456**, 989-992, 2008

Published August 1, 2016

JEM



# Role of neoplastic monocyte-derived fibrocytes in primary myelofibrosis

Srdan Verstovsek,[1] Taghi Manshouri,[1] Darrell Pilling,[4] Carlos E. Bueso-Ramos,[2] Kate J. Newberry,[1] Sanja Prijic,[1] Liza Knez,[1] Ksenija Bozinovic,[1] David M. Harris,[1] Erika L. Spaeth,[1] Sean M. Post,[1] Asha S. Multani,[3] Raajit K. Rampal,[5] Jihae Ahn,[6] Ross L. Levine,[5] Chad J. Creighton,[7] Hagop M. Kantarjian,[1] and Zeev Estrov[1]

Primary myelofibrosis (PMF) is a fatal neoplastic disease characterized by clonal myeloproliferation and progressive bone marrow (BM) fibrosis thought to be induced by mesenchymal stromal cells stimulated by overproduced growth factors. However, tissue fibrosis in other diseases is associated with monocyte-derived fibrocytes. Therefore, we sought to determine whether fibrocytes play a role in the induction of BM fibrosis in PMF. In this study, we show that BM from patients with PMF harbors an abundance of clonal, neoplastic collagen- and fibronectin-producing fibrocytes. Immunodeficient mice transplanted with myelofibrosis patients' BM cells developed a lethal myelofibrosis-like phenotype. Treatment of the xenograft mice with the fibrocyte inhibitor serum amyloid P (SAP; pentraxin-2) significantly prolonged survival and slowed the development of BM fibrosis. Collectively, our data suggest that neoplastic fibrocytes contribute to the induction of BM fibrosis in PMF, and inhibiting fibrocyte differentiation with SAP may interfere with this process.

JCI insight

# Pentraxin-2 suppresses c-Jun/AP-1 signaling to inhibit progressive fibrotic disease

Naoki Nakagawa,[1,2,3] Luke Barron,[4] Ivan G. Gomez,[1,2,4] Bryce G. Johnson,[1,2,4] Allie M. Roach,[1,2,4] Sei Kameoka,[4] Richard M. Jack,[5] Mark L. Lupher Jr.,[5] Sina A. Gharib,[2,6,7] and Jeremy S. Duffield[1,2,4]

[1]Division of Nephrology, Departments of Medicine and Pathology, and [2]Institute of Stem Cell and Regenerative Medicine, University of Washington, Seattle, Washington, USA. [3]Department of Internal Medicine, Asahikawa Medical University, Asahikawa, Japan. [4]Research and Development, Biogen, Cambridge, Massachusetts, USA. [5]Promedior Inc., Lexington, Massachusetts, USA. [6]Computational Medicine Core, [7]Divsion of Pulmonary and Critical Care Medicine, University of Washington, Seattle, Washington, USA.

Pentraxin-2 (PTX-2), also known as serum amyloid P component (SAP/APCS), is a constitutive, antiinflammatory, innate immune plasma protein whose circulating level is decreased in chronic human fibrotic diseases. Here we show that recombinant human PTX-2 (rhPTX-2) retards progression of chronic kidney disease in *Col4a3* mutant mice with Alport syndrome, reducing blood markers of kidney failure, enhancing lifespan by 20%, and improving histological signs of disease. Exogenously delivered rhPTX-2 was detected in macrophages but also in tubular epithelial cells, where it counteracted macrophage activation and was cytoprotective for the epithelium.

Pulmonary Pharmacology & Therapeutics xxx (2013) 1–5

Contents lists available at SciVerse ScienceDirect

Pulmonary Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/ypupt

# Recombinant human serum amyloid P in healthy volunteers and patients with pulmonary fibrosis

M.R. Dillingh [a,*], B. van den Blink [c], M. Moerland [a], M.G.J. van Dongen [a], A. Kleinjan [c], M.S. Wijsenbeek [c], M.L. Lupher Jr. [b], D.M. Harper [b], J.A. Getsy [b], H.C. Hoogsteden [c], J. Burggraaf [a]

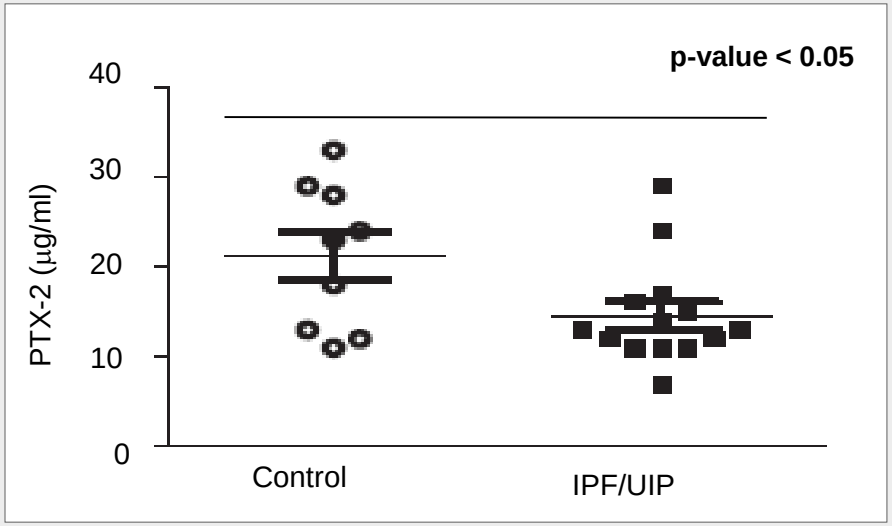
## ABSTRACT

PRM-151, recombinant human Pentraxin-2 (PTX-2) also referred to as serum amyloid P (SAP), is under development for treatment of fibrosis. A First-in-Human (FIH) trial was performed to assess the safety, tolerability, and pharmacokinetics of single ascending intravenous doses of PRM-151 administered to healthy subjects, using a randomized, blinded, placebo controlled study design. Each cohort included three healthy subjects (PRM-151:placebo; 2:1). SAP levels were assessed using a validated ELISA method, non-discriminating between endogenous and exogenous SAP. At a dose level of 10 mg/kg, at which a physiologic plasma level of SAP was reached, two additional healthy volunteers and three pulmonary fibrosis (PF) patients were enrolled enabling comparison of the pharmacokinetic SAP profile between healthy volunteers and PF patients. In addition, the percentage of fibrocytes (CD45+/Procollagen-1+ cells) in whole blood samples was assessed to demonstrate biological activity of PRM-151 in the target population.

PRM-151 administration was generally well tolerated. In two pulmonary fibrosis patients non-specific, transient skin reactions (urticaria and erythema) were observed. PRM-151 administration resulted in a 6- to 13-fold increase in mean baseline plasma SAP levels at dose levels of 5, 10, and 20 mg/kg. The estimated $t_{1/2}$ of PRM-151 in healthy volunteers was 30 h. Pharmacokinetic profiles were comparable between healthy volunteers and PF patients. PRM-151 administration resulted in a 30–50% decrease in fibrocyte numbers 24 h post-dose. This suggests that administration of PRM-151 may be associated with

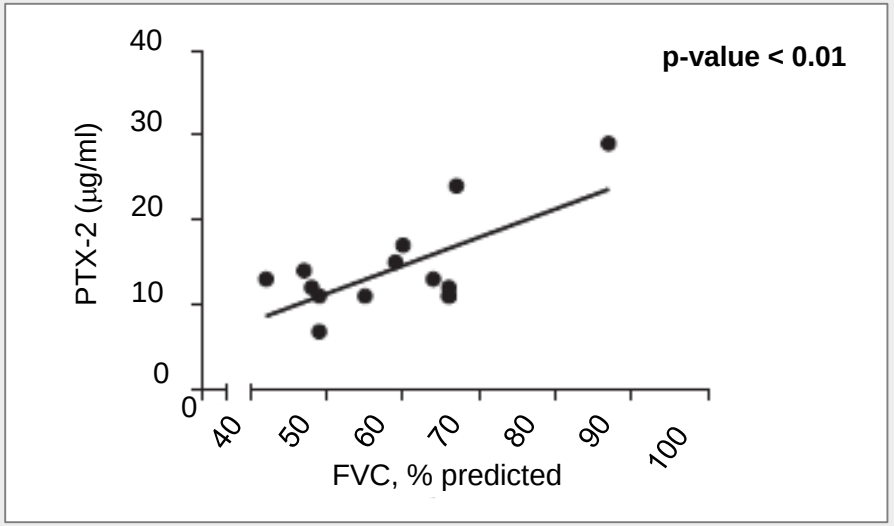
# Endogenous PTX-2 Levels Correlate with Function in IPF Patients

## PTX-2 Serum Levels in IPF Patients vs. Healthy Subjects




➡ **Serum PTX-2 levels are significantly lower in IPF patients than normal controls.**

## PTX-2 Serum Levels in IPF Patients vs. Lung Function




➡ **Higher serum PTX-2 levels in IPF patients directly correlate with greater lung function.**

Murray et al. 2011 *Int J Biochem Cell Biol.* Jan;43(1):154-62.

Eur Respir J 2016; 47: 889–897 | DOI: 10.1183/13993003.00850-2015

ORIGINAL ARTICLE
...TERSTITIAL LUNG DISEASES

# Recombinant human pentraxin-2 therapy in patients with idiopathic pulmonary fibrosis: safety, pharmacokinetics and exploratory efficacy

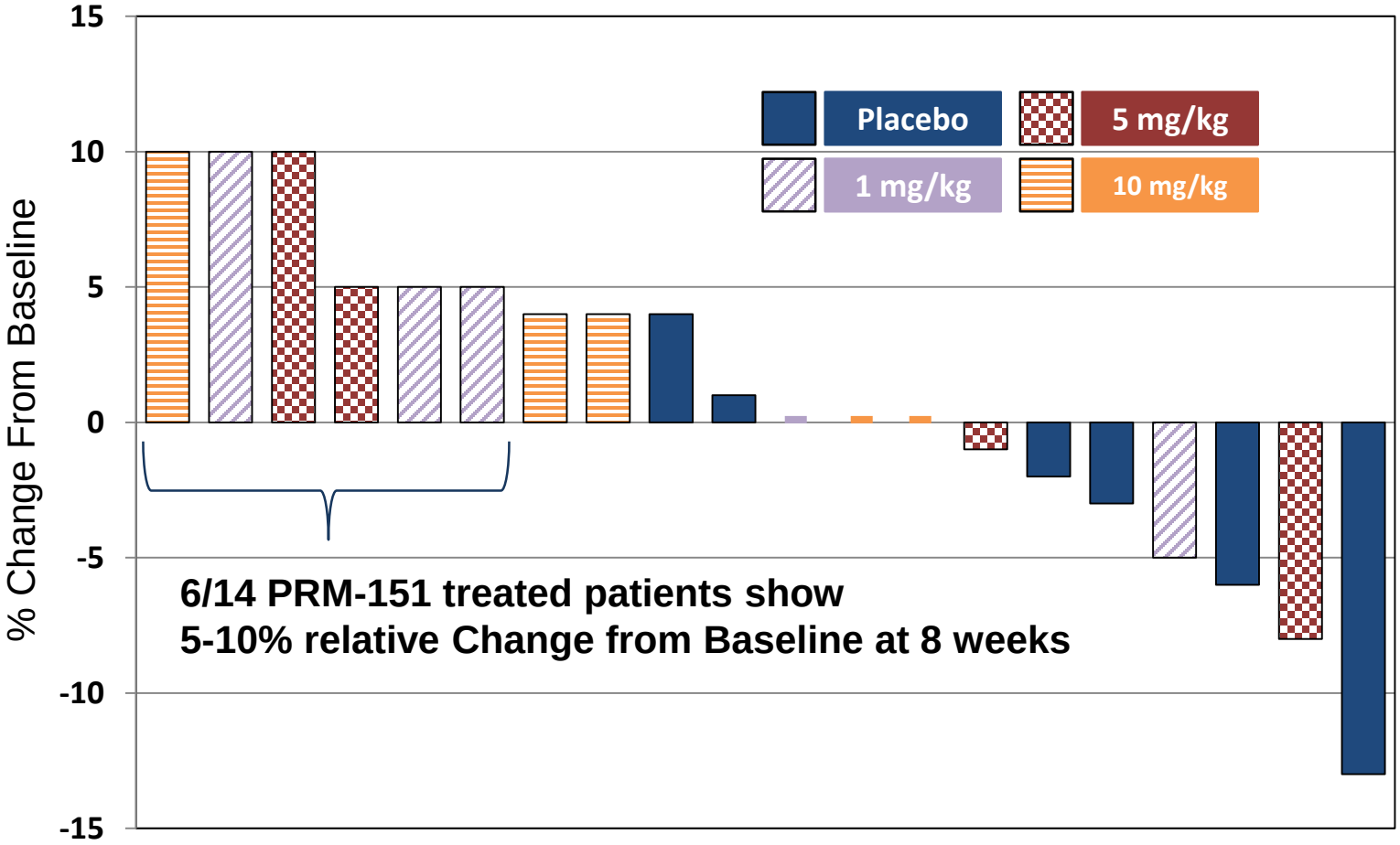
Bernt van den Blink[1], Marlous R. Dillingh[2], Leo C. Ginns[3], Lake D. Morrison[4], Matthijs Moerland[2], Marlies Wijsenbeek[1], Elizabeth G. Trehu[5], Brian J. Bartholmai[6] and Jacobus Burggraaf[2]

A randomised, double-blind, placebo-controlled, multiple ascending dose trial was performed to assess the tolerability and pharmacokinetic and pharmacodynamic characteristics of multiple doses of PRM-151 in IPF patients. Subjects in three successive cohorts (1, 5, or 10 $mg \cdot kg^{-1}$ *versus* placebo) received intravenous study drug on days 1, 3, 5, 8 and 15, and were followed-up to day 57.

PRM-151 was well tolerated at all dose levels, with no serious adverse reactions. Administration of PRM-151 resulted in two- to eight-fold dose-dependent increases in circulating pentraxin-2 levels. Forced vital capacity and 6-min walk test showed trends towards improvement in the combined PRM-151 dose groups. On high-resolution computed tomography scans, stable or improved lung volume unoccupied by interstitial lung abnormality was noted in some PRM-151 subjects compared to placebo subjects on day 57.

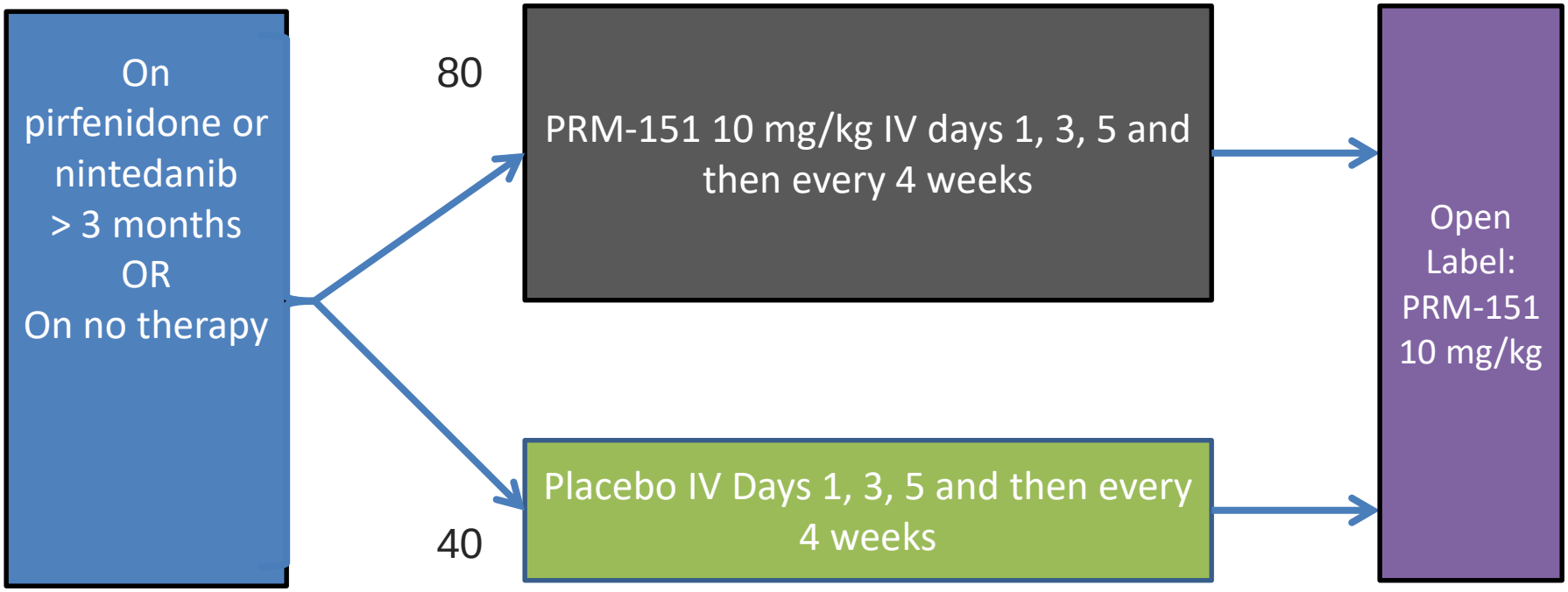
# FVC % predicted relative change from baseline

Mean FVC % predicted *increased* by 2.4% in all PRM-151 treated subjects
Mean FVC % predicted *decreased* by 1.5% in placebo subjects




Eur Respir J 2016; 47: 889–8

# PROMOTE study of PRM-151 in IPF
# Phase 2 Trial in EU and US




- 24 week study treatment | End of Study: week 28 | Optional open label extension (OLE) study
- **Primary objective:** Determine effect size of PRM-151 relative to placebo in change from Baseline to Week 28 in mean FVC% predicted.
- **Secondary endpoints**: Quantitative Image Analysis via HRCT, DLCO, 6MWT, exacerbations.
- **Exploratory endpoints**: Patient Reported Outcome: QOL, cough

A Phase 2 trial of PRM-151 in IPF has fully enrolled in the EU and US

2:1 randomization to PRM-151 vs placebo alone or added to a stable dose of pirfenidone or nintedanib

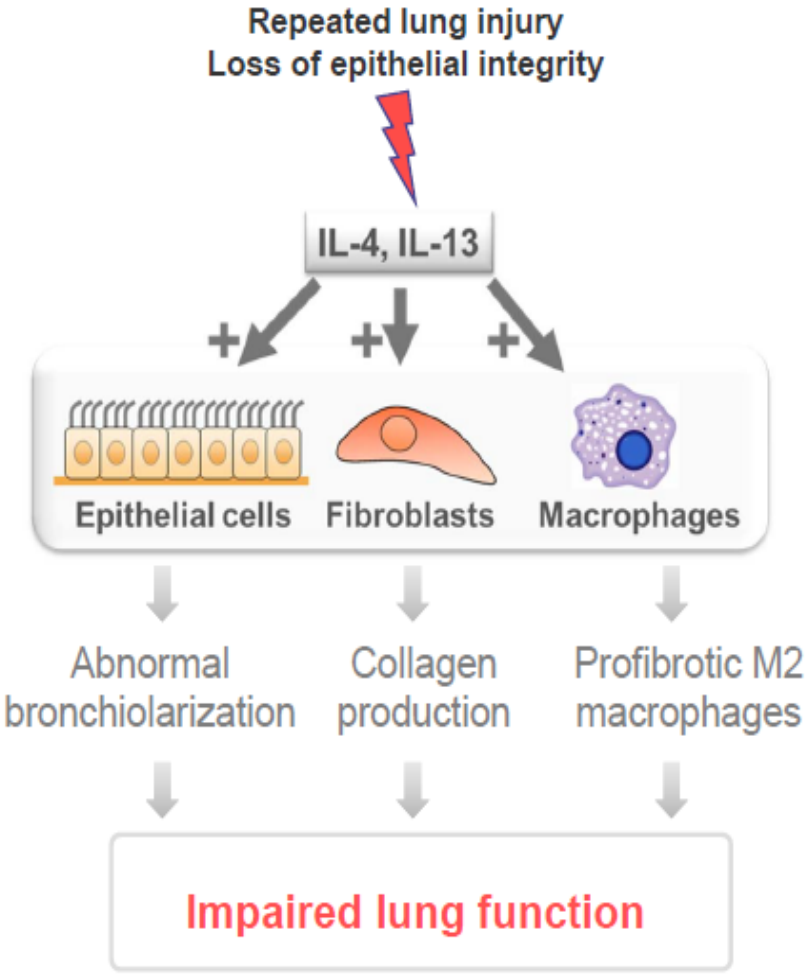
Last patient last visit Expected May 2017

# SAR156597

DRI11772 study (ESTAIR)

# Both IL-4 and IL-13 pathways play key role in IPF pathogenesis

**Courtesy Sanofi**

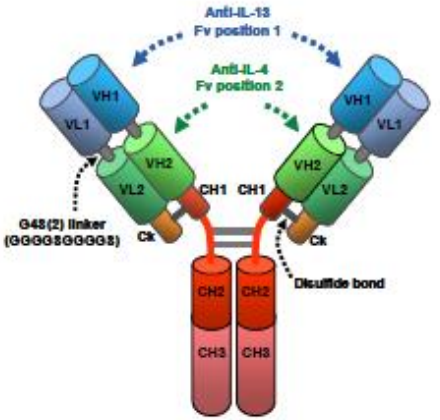



- **In vitro, IL-4/13 promote**
  - Epithelial changes consistent with those associated with abnormal bronchiolarization in airway epithelial cells
  - Differentiation of lung fibroblasts into myofibroblasts and expression of collagen.
  - Differentiation of lung macrophages toward the alternatively-activated (M2) phenotype, which is potentially profibrotic.
- **In animal model of lung fibrosis**
  - Suppression of either IL-4 or IL-13 expression protects against lung fibrosis
- **In patients with IPF**
  - IL-4 and IL-13 are expressed in lung tissue
  - An IL-13-associated mRNA signature was identified in lung biopsies from rapid progressors.
  - Polymorphisms of both IL-4 and IL-13 genes are associated with IPF

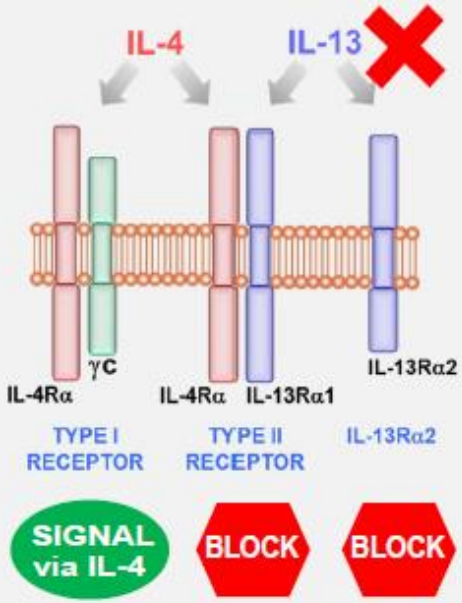
# SAR156597: A novel approach toward a complete blockade of the IL-4 / IL-13 pathways

**Courtesy Sanofi**

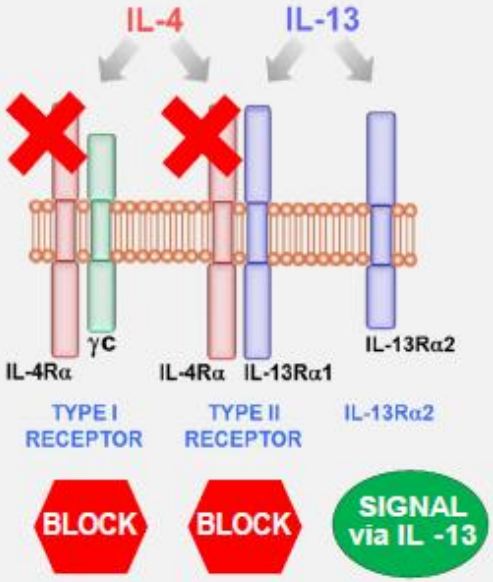
- An engineered bi-specific Ab that targets the cytokines
- Combination of the antigen-binding domains of anti-IL-4 and anti-IL-13 Ab into an innovative single molecule
- Humanized to minimize immunogenicity



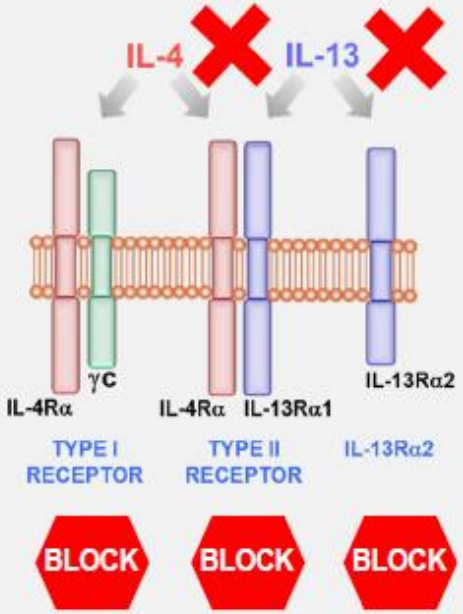

## Antibodies to IL-13 alone (Tralokinumab, Lebrikizumab)




## Antibodies to IL-4Rα (Dupilumab)




## Bi-specific antibody SAR156597



# SAR 156597

Efficacy and safety of SAR156597 in the treatment of Idiopathic Pulmonary Fibrosis (IPF):

*A randomized, double-blind, placebo-controlled,*
*52-week dose-ranging phase 2 study*

*Study ongoing ( enrollment completed )*

# FG-3019 anti-connective tissue growth factor monoclonal antibody: results of an open-label clinical trial in IPF

Ganesh Raghu[1], Mary Beth Scholand[2], João de Andrade[3], Lisa Lancaster[4], Yolanda Mageto[5], Jonathan Goldin[6], Kevin K. Brown[7], Kevin R. Flaherty[8], Mark Wencel[9], Jack Wanger[10], Thomas Neff[11], Frank Valone[11], John Stauffer[11] and Seth Porter[11]

**Affiliations**: [1]University of Washington, Seattle, WA, USA. [2]University of Utah, Salt Lake City, UT, USA. [3]University of Alabama at Birmingham, Birmingham, AL, USA. [4]Vanderbilt University, Nashville, TN, USA. [5]University of Vermont, Burlington, VT, USA. [6]David Geffen School of Medicine, Los Angeles, CA, USA. [7]National Jewish Health, Denver, CO, USA. [8]University of Michigan Health System, USA. [9]Via Christi Clinic, Wichita, KS, USA. [10]Pulmonary Function and Clinical Trial Consultant, Rochester, MN, USA. [11]FibroGen, Inc., San Francisco, CA, USA.

**Correspondence**: Ganesh Raghu, Division of Pulmonary and Critical Care Medicine, Campus Box 356522, Seattle, WA 98195-6522, USA. E-mail: graghu@u.washington.edu.

ABSTRACT FG-3019 is a fully human monoclonal antibody that interferes with the action of connective tissue growth factor, a central mediator in the pathogenesis of fibrosis.

This open-label phase 2 trial evaluated the safety and efficacy of two doses of FG-3019 administered by intravenous infusion every 3 weeks for 45 weeks in patients with idiopathic pulmonary fibrosis (IPF). Subjects had a diagnosis of IPF within the prior 5 years defined by either usual interstitial pneumonia (UIP) pattern on a recent high-resolution computed tomography (HRCT) scan, or a possible UIP pattern on HRCT scan and a recent surgical lung biopsy showing UIP pattern. Pulmonary function tests were performed every 12 weeks, and changes in the extent of pulmonary fibrosis were measured by quantitative HRCT scans performed at baseline and every 24 weeks.

FG-3019 was safe and well-tolerated in IPF patients participating in the study. Changes in fibrosis were correlated with changes in pulmonary function.

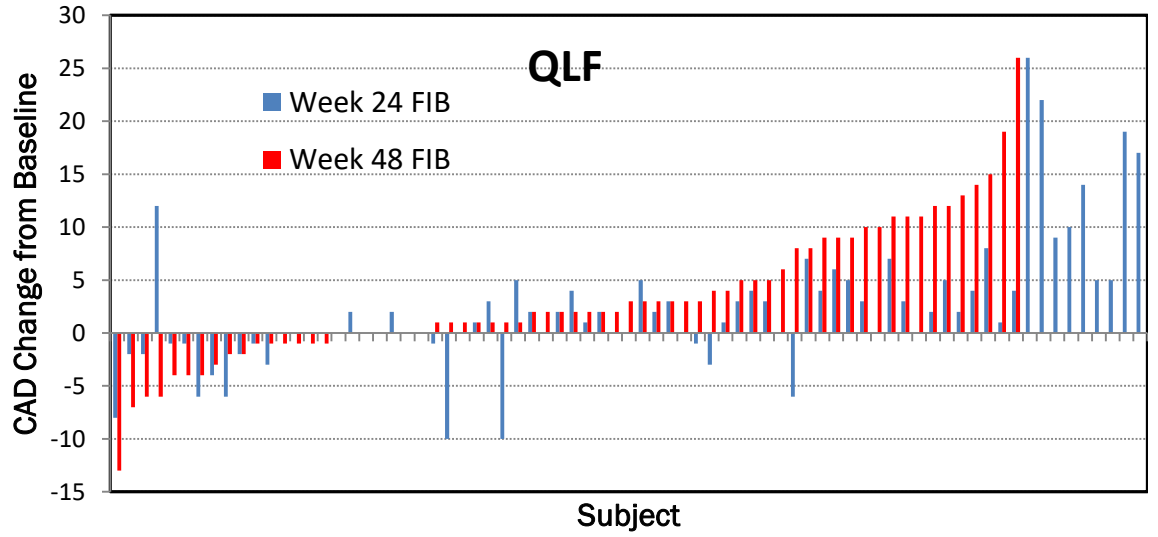
Further investigation of FG-3019 in IPF with a placebo-controlled clinical trial is warranted and is underway.

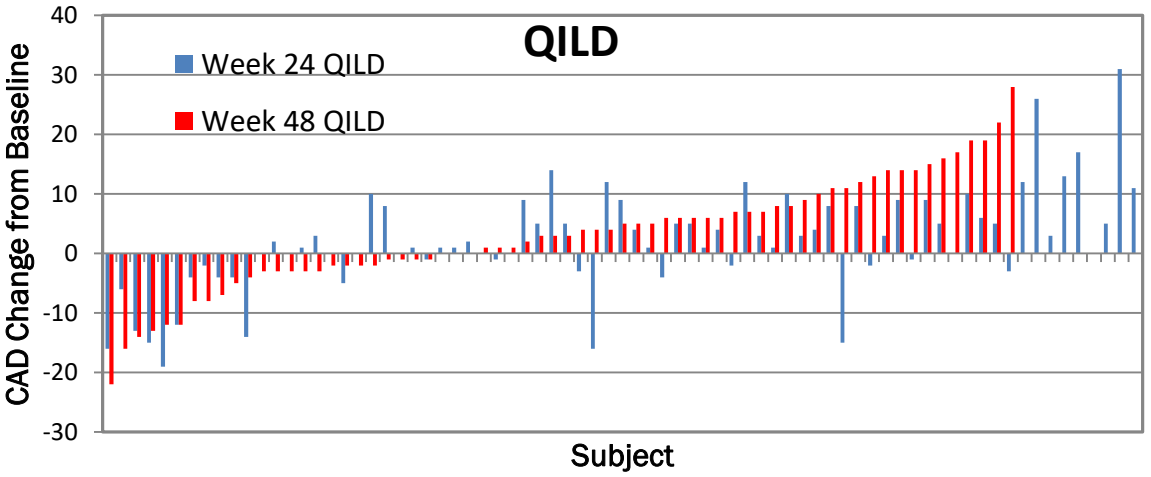
@ERSpublications
**FG-3019 demonstrated good outcomes in changes in pulmonary function and extent of pulmonary fibrosis in IPF** http://ow.ly/Xn7B4

**Raghu et al ERJ 2016**

# Substantial Subsets In Cohorts 1 and 2 Show Improved or Stable Fibrosis at 24 and 48 Weeks

Δ CAD = % change from BL in Computer-Aided Detection scores assessed at ■ 24 & ■ 48 weeks



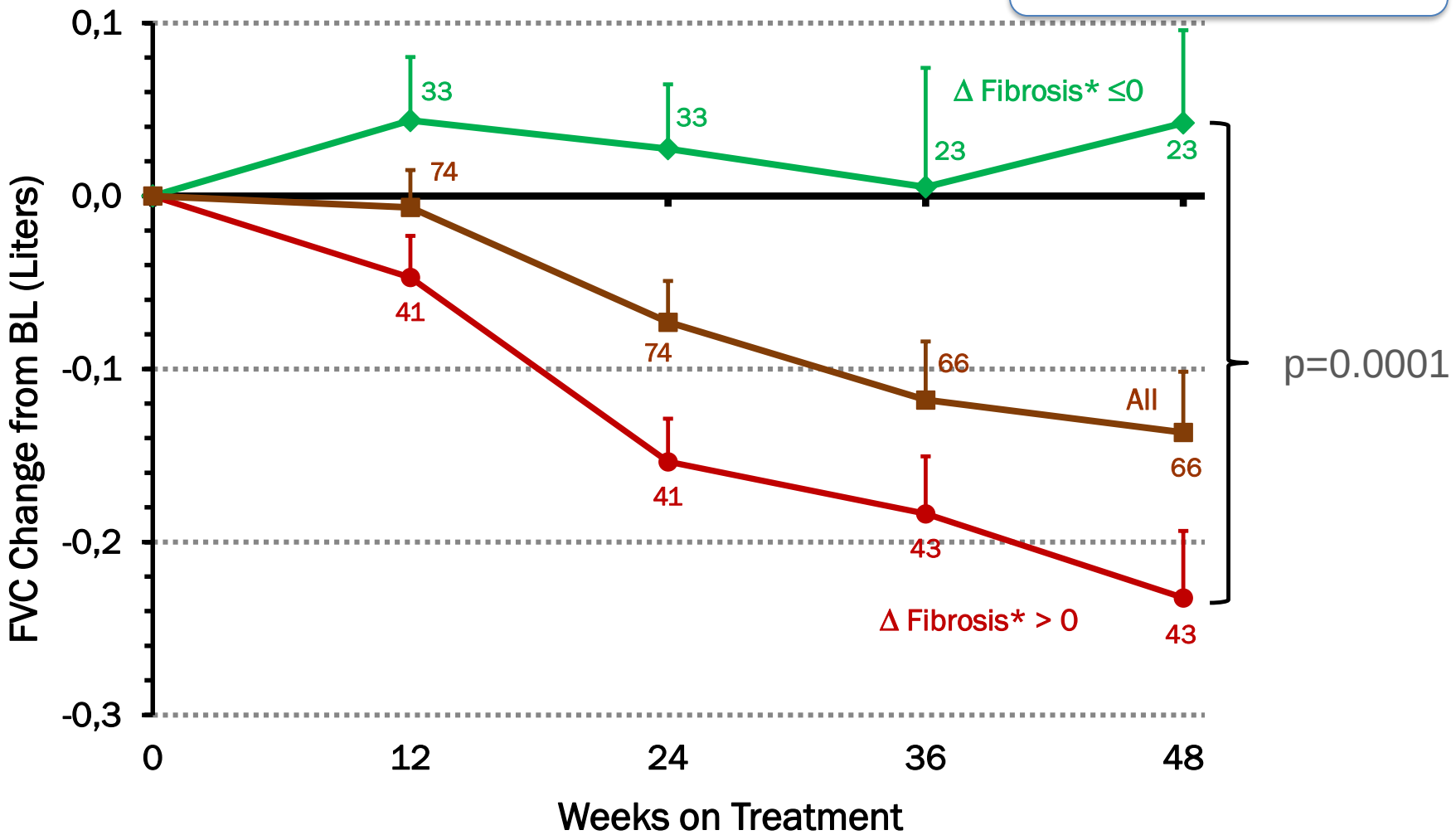

Improved

Worse

Raghu et al
ERJ 2016

# Stable or Improved Fibrosis was Associated with Improved FVC

Raghu et al ERJ 2016




* Categorical changes in FVC at Weeks 12 and 24 were based on Week 24 change in fibrosis, and for Weeks 36 and 48 they were based on Week 48 change in fibrosis.

# PRAISE Trial Overview

## **Main Study:** Double-blind, randomized, placebo-controlled trial

- Dosing: 30 mg/kg IV every 3 weeks for a total of 16 doses / 45 weeks or matching placebo
- Mild to moderate IPF patients
- Main Assessments
  - Tolerability and safety mainly through AE collection
  - Efficacy; lung function (FVC) and lung fibrosis (qHRCT)
- Periods
  - Randomized 48 weeks period
  - Extension open-label periods (voluntary)
    - Placebo arm: additional 16 doses (45 weeks) for all subjects
    - Active arm: continue treatment for as long as subjects show benefit from drug

## **Substudy:** Trial enrichment with subjects on open-label background IPF SoC

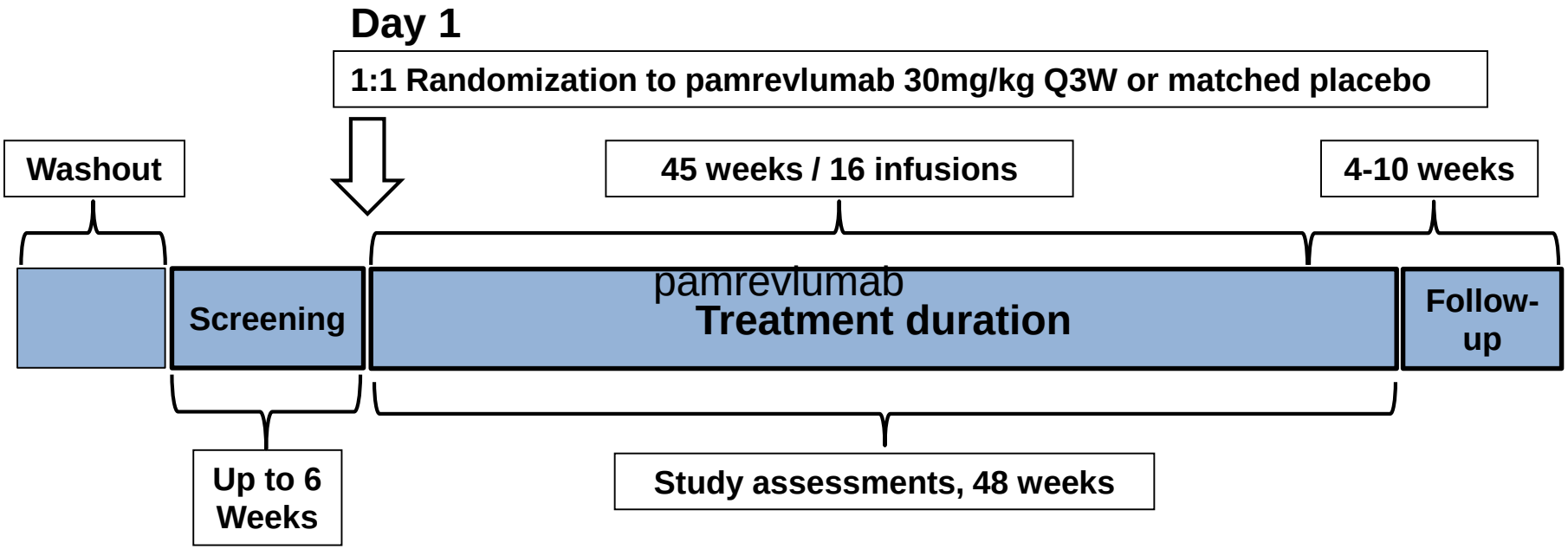
- 1:1 Stratification to pirfenidone or nintedanib
- Same dosing regimen for a total of 8 doses / 21 weeks
- Same safety and efficacy assessments plus PK

**Centralized FVC, DLCO and HRCT reading**
**DMC for safety review**

# Pamrevlumab:

## Monoclonal antibody against CTGF

### Randomized, double-blind, placebo controlled trial




Main assessments:

- FVC: BL and weeks 12, 24, 36 and 48
- qHRCT: BL and weeks 24 and 48

# PANTHER(NAC)-IPF

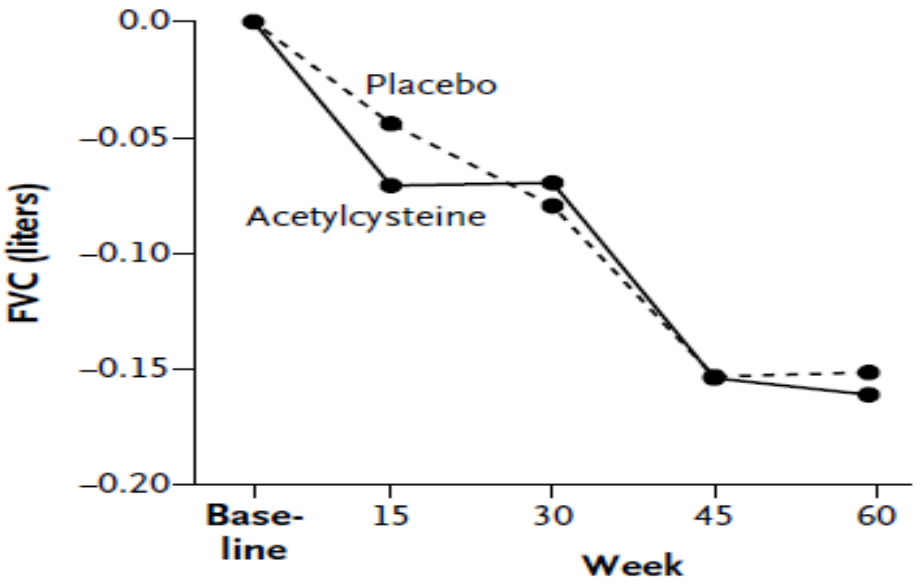
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Randomized Trial of Acetylcysteine in Idiopathic Pulmonary Fibrosis

The Idiopathic Pulmonary Fibrosis Clinical Research Network*

**Idiopathic Pulmonary Fibrosis Clinical Research Network.**
**N Engl J Med 2014;370:2093–101.**




| No. at Risk | | | | | |
|---|---|---|---|---|---|
| Acetylcysteine | 133 | 127 | 118 | 113 | 102 |
| Placebo | 131 | 127 | 119 | 118 | 109 |

# Idiopathic pulmonary fibrosis

## PANTHER-IPF(NAC)-IPFnet trial-NEJM 2014

- Lessons learned
  -no effect on decline in FVC over one yr with use of NAC
  -some positive signals with use of NAC( mental well being; walk distance)
- Some differences in effects in patients enrolled pre and post “alert” disclosed with the use of prednisone plus azathioprine plus NAC

- Unresolved questions

# Combination therapy: the future of management for idiopathic pulmonary fibrosis?

*Wim A Wuyts, Katerina M Antoniou, Keren Borensztajn, Ulrich Costabel, Vincent Cottin, Bruno Crestani, Jan C Grutters, Toby M Maher, Venerino Poletti, Luca Richeldi, Carlo Vancheri, Athol U Wells*

***Lancet Resp Med* 2014; 11: 933-42**

# Safety and tolerability of acetylcysteine and pirfenidone combination therapy in idiopathic pulmonary fibrosis: a randomised, double-blind, placebo-controlled, phase 2 trial

Jürgen Behr, Elisabeth Bendstrup, Bruno Crestani, Andreas Günther, Horst Olschewski, C Magnus Sköld, Athol Wells, Wim Wuyts, Dirk Koschel, Michael Kreuter, Benoît Wallaert, Chin-Yu Lin, Jürgen Beck, Carlo Albera

**Interpretation** Findings from the PANORAMA study suggest that addition of acetylcysteine to pirfenidone does not substantially alter the tolerability profile of pirfenidone, and is unlikely to be beneficial in IPF.

Lancet Respir Med 2016; 4: 445–53

Published Online May 5, 2016 http://dx.doi.org/10.1016/S2213-2600(16)30044-3

# The Panorama study

Lancet Respir Med 2016;
4: 381–89
Published Online
March 31, 2016
http://dx.doi.org/10.1016/

Comment

Marlies S Wijsenbeek, *Harold R Collard

# Acetylcysteine in IPF: the knockout blow?

Acetylcysteine (also known as n-acetylcysteine or NAC) is an antioxidant precursor to glutathione, the body's primary endogenous antioxidant. Historically used for the treatment for cystic fibrosis and paracetamol overdose, acetylcysteine has more recently been studied as an antifibrotic.[1] In 2005, a landmark study of patients with the fibrotic lung disease idiopathic pulmonary fibrosis (IPF) demonstrated a slowing of physiological decline when oral acetylcysteine was added to standard of care at that time (prednisone and azathioprine).[2] Largely on the basis of these results, oral acetylcysteine (as monotherapy or in combination with prednisone and azathioprine) was endorsed by the 2011 international IPF guidelines as "a reasonable choice in a minority" of patients.[3] It has been widely used for the treatment of IPF.

Unfortunately, the story of acetylcysteine in IPF has since become more complicated. A follow-up study comparing oral acetylcysteine (both as monotherapy and or placebo for 24 weeks; 122 patients were included in the analysis. This was a safety and tolerability study, but efficacy endpoints including forced vital capacity (FVC), 6 min walk test distance, and dyspnoea scores were also recorded. There are two key results. First, the acetylcysteine plus pirfenidone group had an increased incidence of photosensitivity compared with pirfenidone alone (eight [13%] patients *vs* one [2%] patient; mean difference 11·7% [95% CI 2·6–20·9], p=0·016). Second, the acetylcysteine plus pirfenidone group demonstrated more rapid disease progression as measured by change in FVC. The adjusted rate of FVC decline in the acetylcysteine plus pirfenidone group was 126 mL over 24 weeks—more than three times the rate of decline seen in the pirfenidone-only group (between-group difference 91 mL [95% CI −174·4 to −8·3], p=0·031). Importantly, there is no mechanistic explanation offered for this finding. No significant between-group differences were seen in the

Liam Norris/Science Photo Library

*Lancet Respir Med* 2016
Published Online
May 5, 2016
http://dx.doi.org/10.1016/S2213-2600(16)30085-6
See Online/Articles
http://dx.doi.org/10.1016/S2213-2600(16)30044-3

# N-ACETYL CYSTEINE FOR IPF

## – *the door is still open*

Ganesh Raghu, Imre Noth and Fernando Martinez (The Lancet Resp Med ; in press)

- The PANORAMA TRIAL : major concerns
- Designed to addresses the tolerability of the combined treatment as the primary endpoint and not designed to determine the efficacy of the combined treatment of NAC and pirfenidone
- The authors extrapolate the findings based on a post hoc and exploratory analyses of the slope of the FVC decline from 12 weeks to 24 weeks (Pirfenidone plus NAC , N=17;pirfenidoneplus placebo ,N=18) The rate of FVC decline of 34mls in the Pirfenidone alone group translates into only 1.2% while the Pirfenidone with NAC arm translates into a 4.5%
- limited sample size in the PANORAMA trial, this observation is underpowered and interpretation should be taken with caution
- one must be cautious with over interpreting the data generated from post hoc and exploratory analyses must be considered as hypothesis generating

Johnson WC, Raghu G. Clinical trials in idiopathic pulmonary fibrosis: A word of caution concerning choice of outcome measures. *Eur Respir J*. 2005; **26**: 755-758.

# N-ACETYL CYSTEINE FOR IPF

## – *the door is still open*

Ganesh Raghu, Imre Noth and Fernando Martinez (The Lancet Resp Med ; in press)

- The PANORAMA TRIAL : major concerns

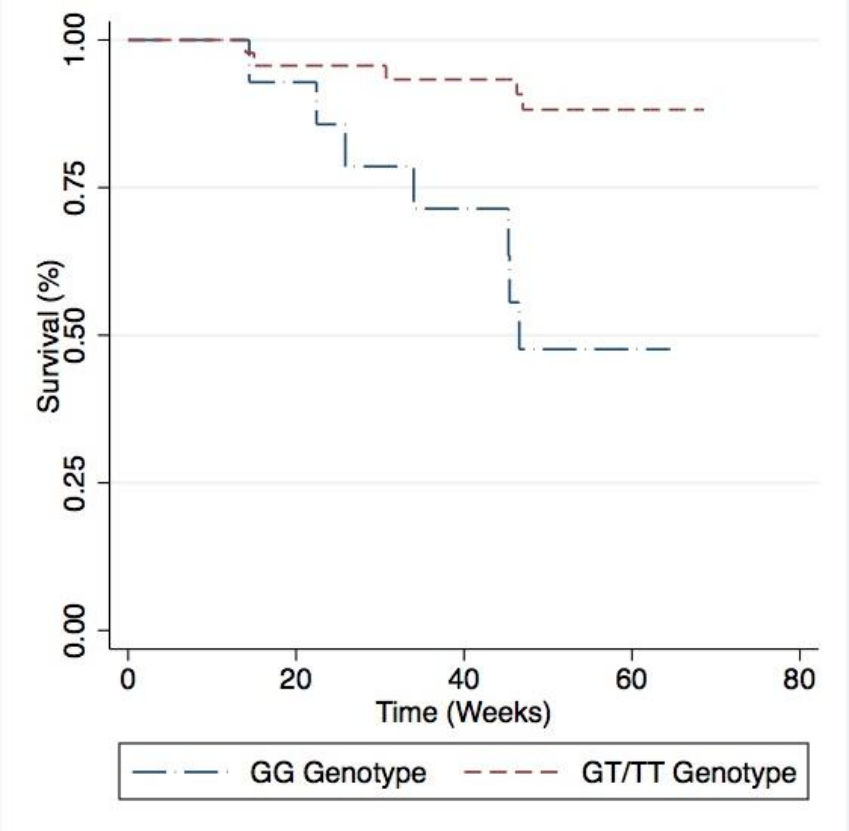
- Designed to addresses the tolerability of the combined treatment as the primary endpoint and not designed to determine the efficacy of the combined treatment of NAC and pirfenidone

- *"To throw the baby out with the bathwater"* is not what one should do based on extrapolated conclusions from studies with different pre specified endpoint.

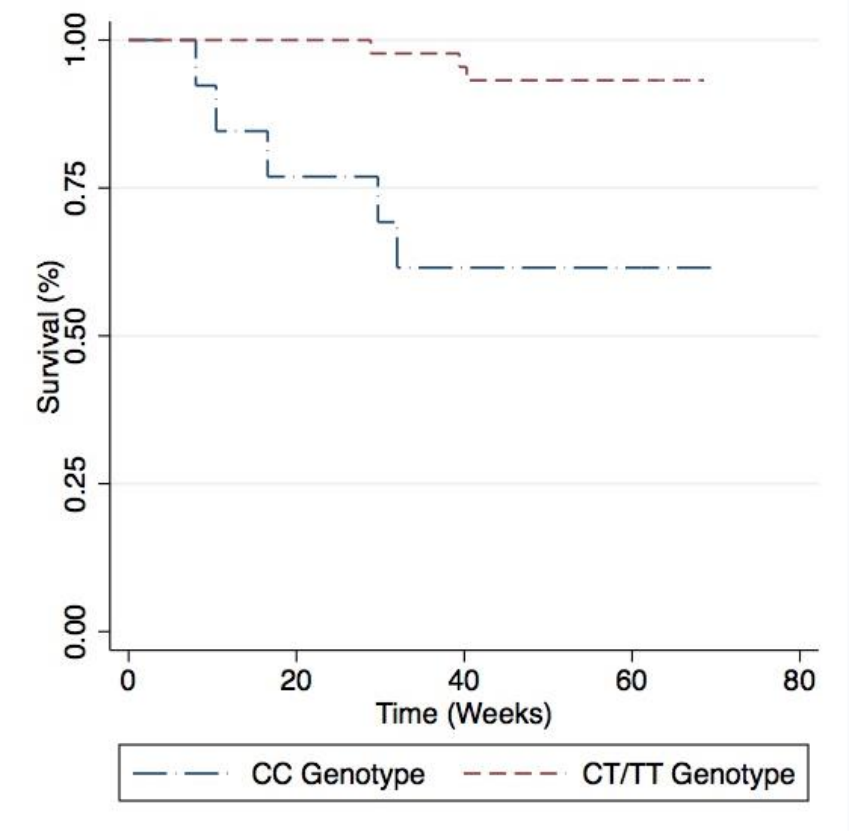
- *Only a prospective randomized clinical trial of NAC in patients stratified by genotypes can determine the safety and efficacy of NAC in the subgroups using endpoints that are clinically meaningful to patients beyond FVC alone as an endpoint.*

# NAC effect on progression free survival depends on MUC5B and TOLLIP genotype

**rs35705950 (MUC5B)**




**rs3750920 (TOLLIP)**




Oldham et al *AJRCCM 2015*

# Idiopathic pulmonary fibrosis(IPF)

## Published Reports of Clinical trials : 1991-

## Lessons learned

- ***Bench-to-bedside : what works/ed at the bench and is biologically plausible does not necessarily work at the bedside***
- Other than standard physiological /clinical assessment of disease progression, no other cellular/molecular/genetic biomarkers have been utilized to stratify treatment in clinical trials

- *…but recent pharmacogenomic data from a subgroup of patients participating in PANTHER trial is encouraging for use of NAC in some patients - ( Oldham et al AJRCCM, 2015 )*

# Idiopathic pulmonary fibrosis(IPF)

- The new Era of IPF :  2017 –

- *New perspectives in IPF therapy: hopes and questions*

# Application of Mesenchymal Stem Cells to Patients with IPF*

**A Phase I Trial**

**to Evaluate the Safety, Tolerability, and Potential Efficacy of**

**Human Mesenchymal Stem Cell Infusion in patients with**

**Idiopathic Pulmonary Fibrosis**

*Completed : safe and moving to phase 2
Marilyn K. Glassberg Csete : PI
CHEST 2017(in press)

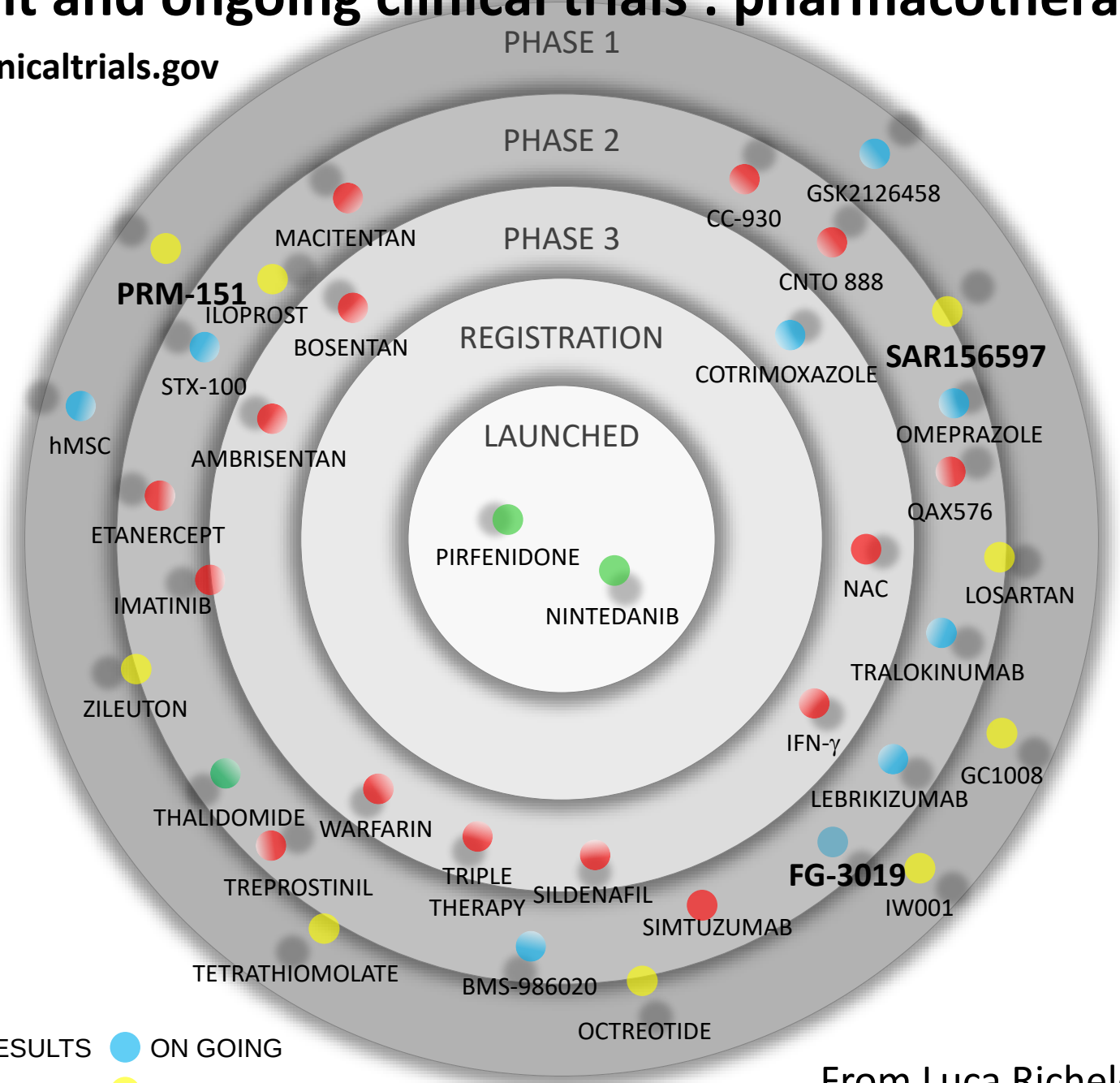
* Clinicaltrials.gov Identifier: NCT02013700; IND 15205

# IPF treatment :
# New concepts: precision medicine

- NAC
- Telomeres
- Relaxin

# Recent and ongoing clinical trials : pharmacotherapy

**www.clinicaltrials.gov**




POSITIVE RESULTS ON GOING
NEGATIVE RESULTS PENDING RESULTS

From Luca Richeldi(courtesy)

# IPF- some, ongoing /initiated clinical trials clinical trial.gov

- Serum Amyloid P/Pentraxin-2( PROMOTE Trial; Promedior)
- IL4/IL13 ( ESTAIR Trial, SANOFI)
- CTGF(PRAISE  Trial; Fibrogen )

- WRAP –IPF- anti GER concept ( NIH, USA)
- CLEAN UP-IPF –antimicrobial concept ( NIH ,USA) +? Italian consortium

# Study of Clinical Efficacy of Antimicrobial Therapy Strategy Using Pragmatic Design in Idiopathic Pulmonary Fibrosis (CleanUP IPF)

Fernando J. Martinez
Kevin J. Anstrom
Imre Noth

Michael Durheim
Harold Collard
Kevin Flaherty
Brett Ley
Ganesh Raghu
Jamie Sheth
Xiaoping Wu

# CLEAN UP –IPF BACKGROUND

- A small IPF randomized trial suggested improved clinical outcomes with co-trimoxazole
- Several small IPF studies suggest improved lung function and symptoms with doxycycline
- Genetic substrate may influence therapeutic responsiveness in IPF patients

# CLEAN UP -IPF

# HYPOTHESIS

***Antimicrobial therapy in IPF patients will improve clinical outcomes in a pragmatic therapeutic trial***

# CLEAN UP –IPF
## STUDY AIMS

- To determine that antimicrobial therapy (co-trimoxazole or doxycycline) improves the time to respiratory hospitalization or death
- To determine if response to antimicrobial therapy is a function of genetic susceptibility to impaired host response in IPF patients.

# CLEAN UP-IPF
## POPULATION

- Given pragmatic goals:
  - we wish to recruit as representative an IPF population as possible (age, gender, ethnic background, socioeconomic status, comorbidity)
  - we wish to minimize subject and site burden
  - we wish to minimize subject risk given limited in person follow-up
  - we wish to maximize the likelihood of positive study outcomes

# CLEAN UP-IPF INTERVENTIONS (1)

- **Randomize to oral antimicrobial therapy in addition to standard-of-care or standard-of-care alone.**
- Antimicrobial therapy will be:
  - trimethoprim 160mg /800mg sulfamethoxazole (double strength co-trimoxazole) twice a day plus folic acid 5 mg daily unless there is a contraindication to this therapy.
  - if intolerant to co-trimoxazole the dosage can be decreased to once a day 160mg trimethoprim/800mg sulfamethoxazole (double strength co-trimoxazole) three times weekly plus folic acid 5 mg daily.
  - if intolerance continues then the antimicrobial agent can be changed to doxycycline. Doxycycline will be dosed at 100 mg once daily if body weight is < 50 kg and 100 mg twice daily if $\geq$ 50 kg.

# CLEAN UP-IPF PRIMARY OUTCOME MEASURES

Time to from randomization to first respiratory hospitalization or all-cause mortality

# CLEANUP-IPF : What have we been doing?

- Addressing multiple issues:
  - 1) Feasibility
  - 2) Operations
  - 3) Biological sample collection

# CLEAN UP-IPF : Feasibility:

- Multiple fronts:
  - Creation of Italian consortium and submitting grant to *Agenzia Italiana del Farmaco* – propose to recruit 200 subjects

# CLEAN UP-IPF : Italian Consortium*( TENTATIVE):


coordinator: Luca Richeldi

# Ganesh Raghu : the Lancet Resp Med May 2016



# Idiopathic pulmonary fibrosis: combating on a new turf

Pulmonary fibrosis of unknown aetiology was first described by Hamman and Rich in 1933, and adults with fibrotic lung disease of unknown cause were later considered to have cryptogenic fibrosing alveolitis. However, in 2000 a consensus of experts defined idiopathic pulmonary fibrosis as a distinct entity,[1] with the diagnostic criteria and the natural course of idiopathic pulmonary fibrosis being more precisely described in 2011.[2] The histological and radiological criteria for usual interstitial pneumonia (a diagnostic hallmark of idiopathic pulmonary fibrosis) allowed the enrolment of patients with well-defined idiopathic pulmonary fibrosis into clinical trials worldwide. Patients

Substantial new evidence led to an update of treatment guidelines for idiopathic pulmonary fibrosis in 2015.[10] Patients are now being spared the harmful effects from treatment with prednisone, azathioprine, and N-acetylcysteine.[5] The war to combat idiopathic pulmonary fibrosis has begun on new turf with patients being treated with the novel antifibrotic drugs pirfenidone and nintedanib, which decrease the rate of decline in forced vital capacity over a year in patients with mild to moderate impairment at baseline.[5–8] Although this is a small step towards conquering idiopathic pulmonary fibrosis, treatment regimens are needed that improve survival, with the aim of an eventual cure. For

Science Photo Library

*Lancet Respir Med* 2016

Published Online
May 10, 2016
http://dx.doi.org/10.1016/S2213-2600(16)30106-0

# IPF- some, ongoing /initiated clinical trials clinical trial.gov

- Serum Amyloid P/Pentraxin-2( PROMOTE Trial; Promedior)
- IL4/IL13 ( ESTAIR Trial, SANOFI)
- CTGF(PRAISE  Trial; Fibrogen )

- WRAP –IPF- anti GER concept ( NIH, USA)
- CLEAN UP-IPF –antimicrobial concept ( NIH ,USA) +? Italian consortium

# Idiopathic pulmonary fibrosis(IPF)
## Published Reports of Clinical trials : 1991-

Lessons learned

- Unmet need – treatment met( modest)
- Kudos to IPF community at large : CONGRATULATIONS !!
- Landscape for Clinical Management : NEW TURF
- New trials : combination, sequential, stratified by biomarkers, pharmocogenomics, personalized medicine, pragmatic trials
- **The war against IPF – to combat IPF has just begun !**

# Acknowledgements

***Patients and supporting care givers***

- **sponsors, donors**
- **investigators, coordinators,**
- **care providers**
- **Colleagues, peers, critiques**
- **patient advocacy and support groups**
- **families**

Thank You