From Pipette to Patient:
An update on the IPF treatment landscape

Robert Hallowell, M.D.

Clinical Pulmonary Director

Beth Israel Deaconess Medical Center

July 15th, 2020

Beth Israel Deaconess Medical Center

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

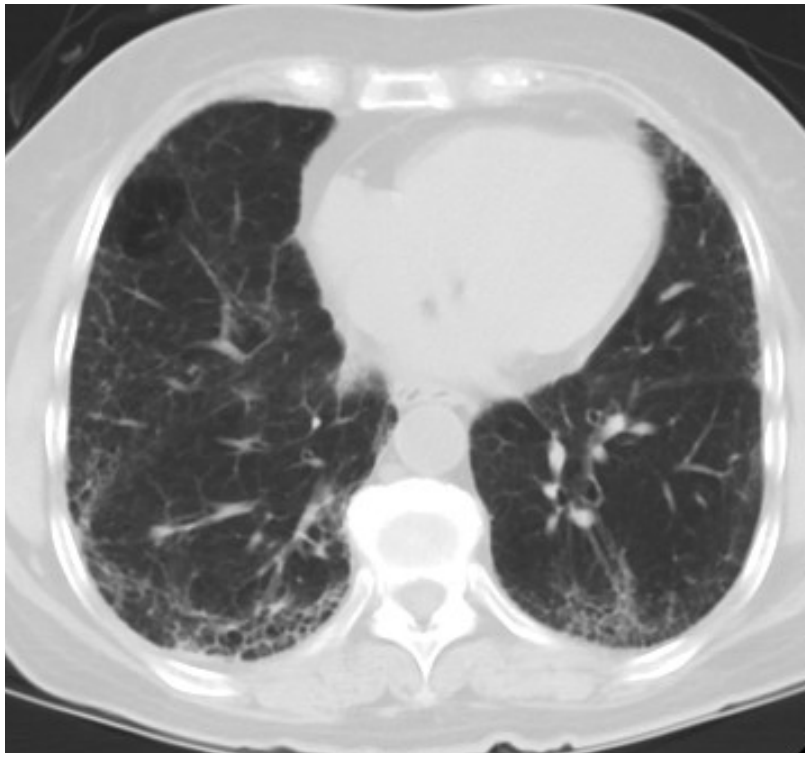
Disclosures

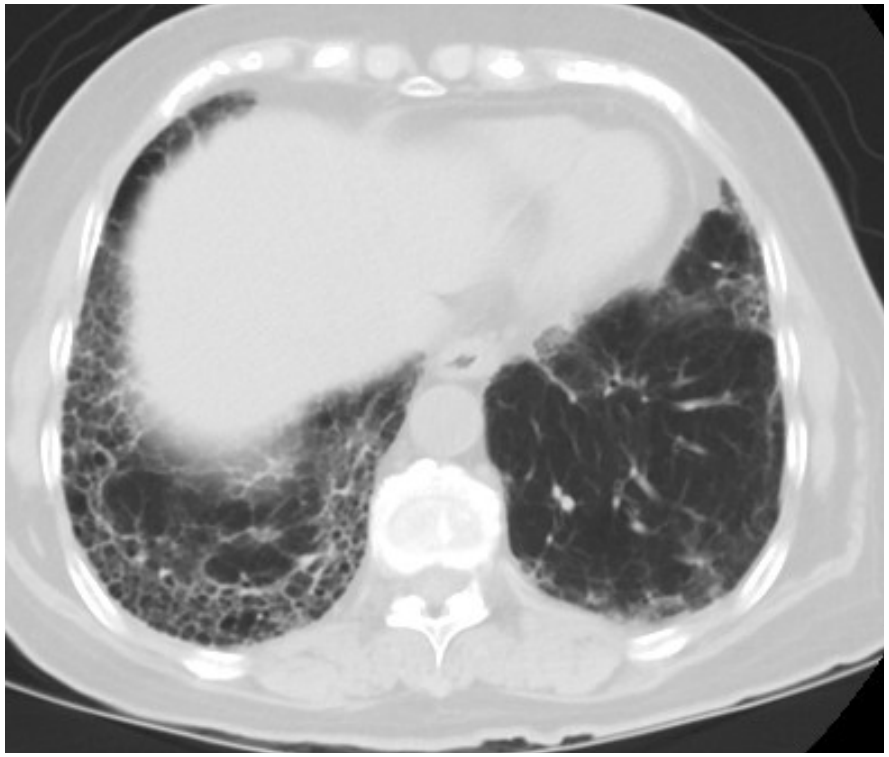
- I have not received funds from any drug company for this lecture

- I *will* give each company credit by name for their innovative work throughout the talk

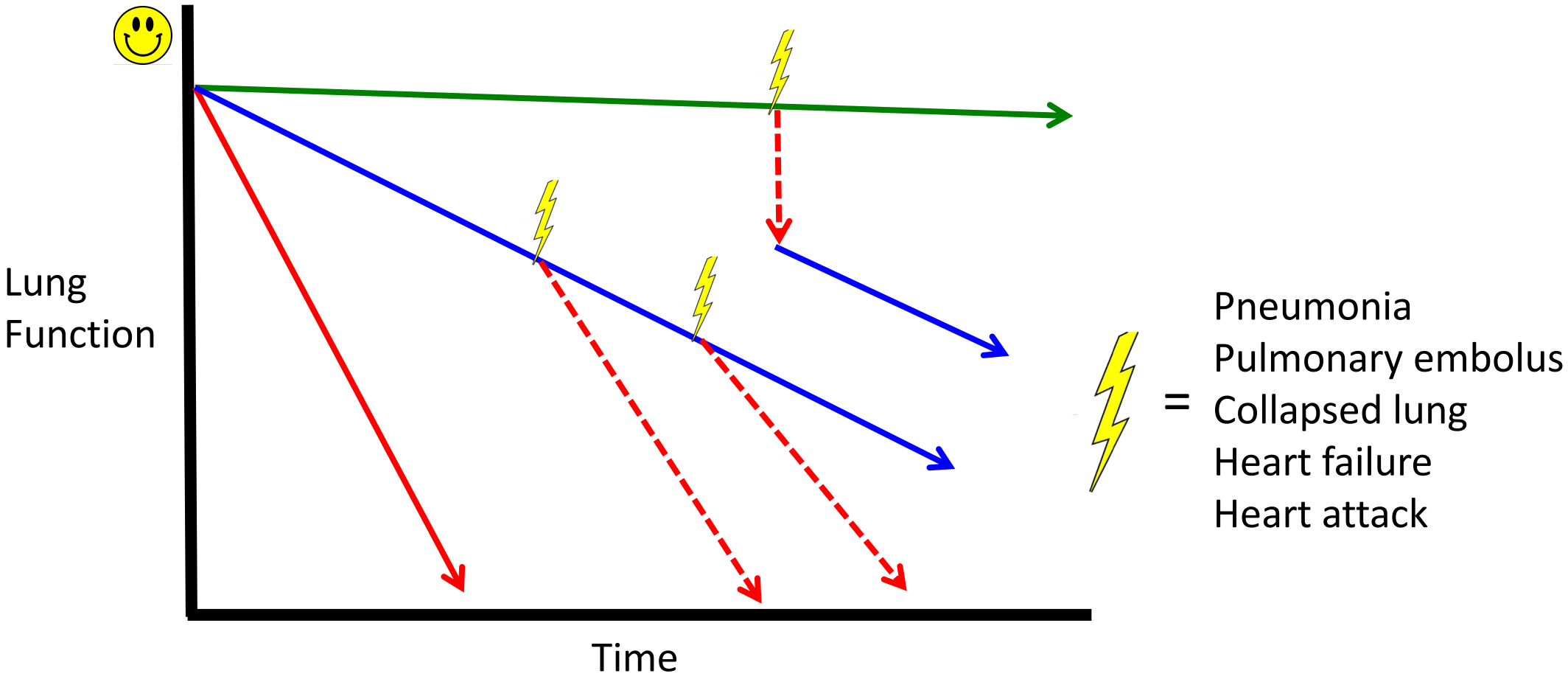
73 year-old man with 20 pack-years of smoking

18 months of dry cough and slowly progressive DOE





Natural Course of IPF

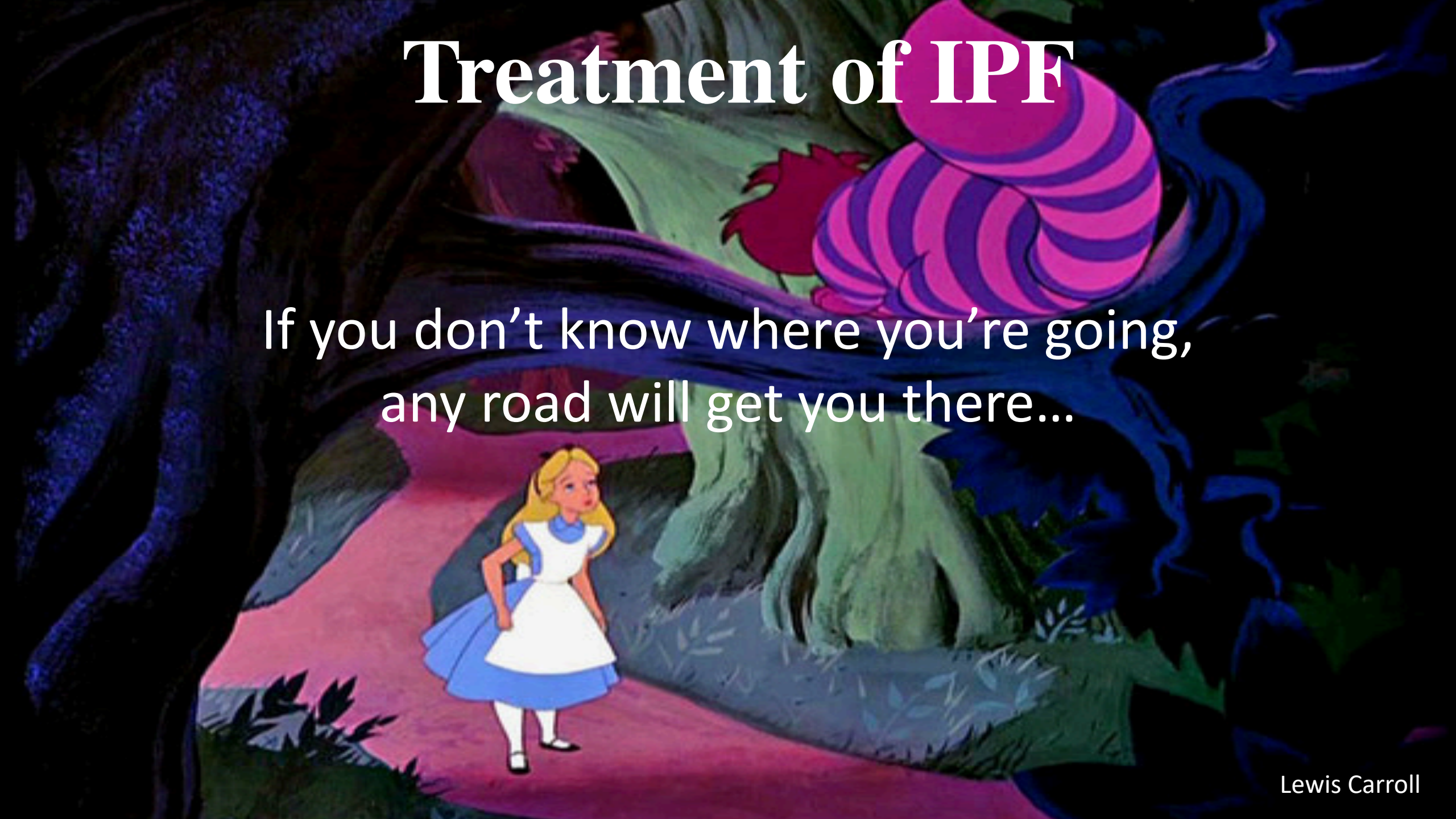


Median survival: 3 years from diagnosis **(probably higher now)**

Acute worsening: 5-10% annually

Am J Respir Crit Care Med Vol 183. pp 788–824, 2011

Treatment of IPF



If you don’t know where you’re going,
any road will get you there…

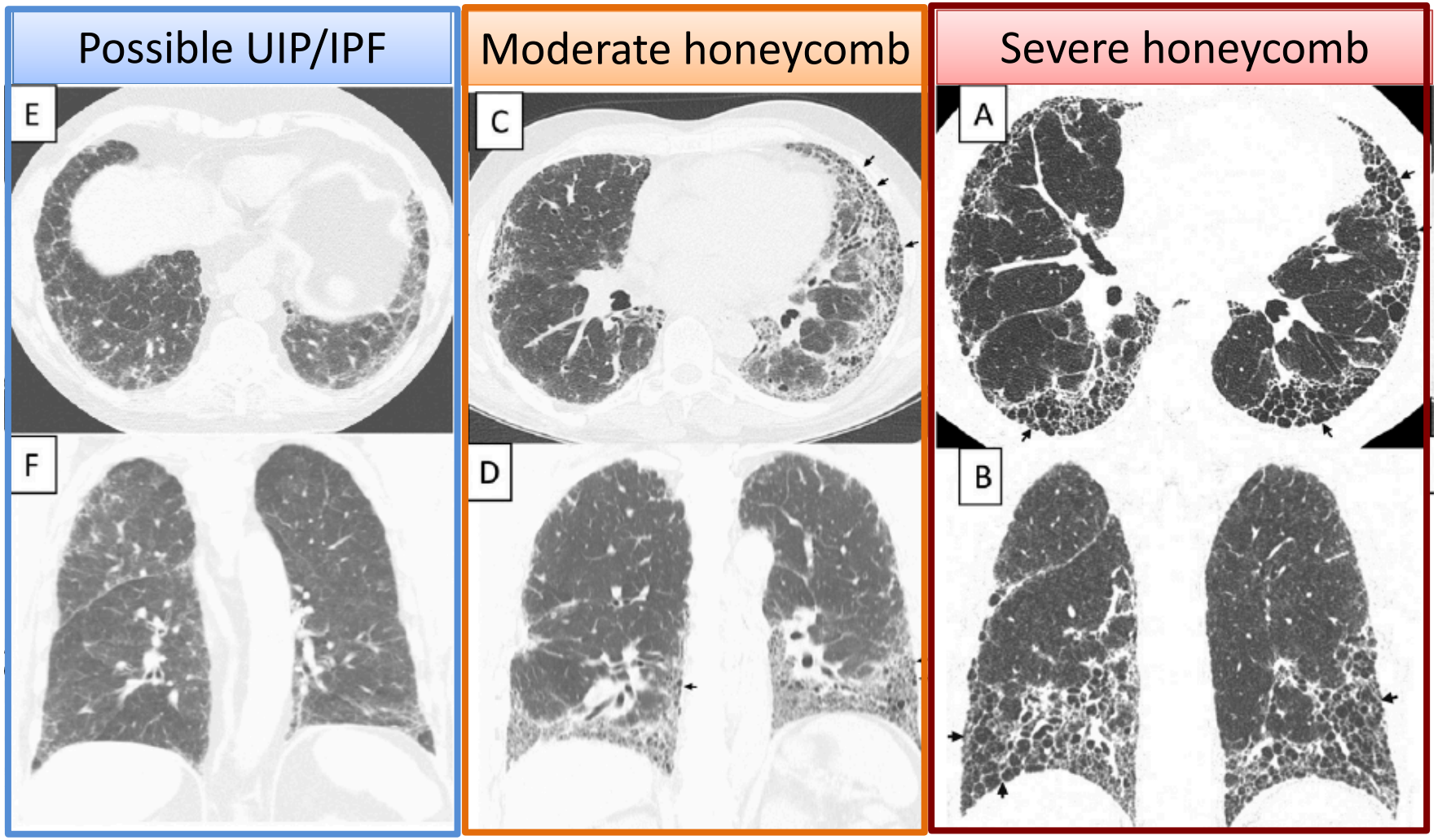
Lewis Carroll

Failed therapies prior to the current age of anti-fibrotic medications

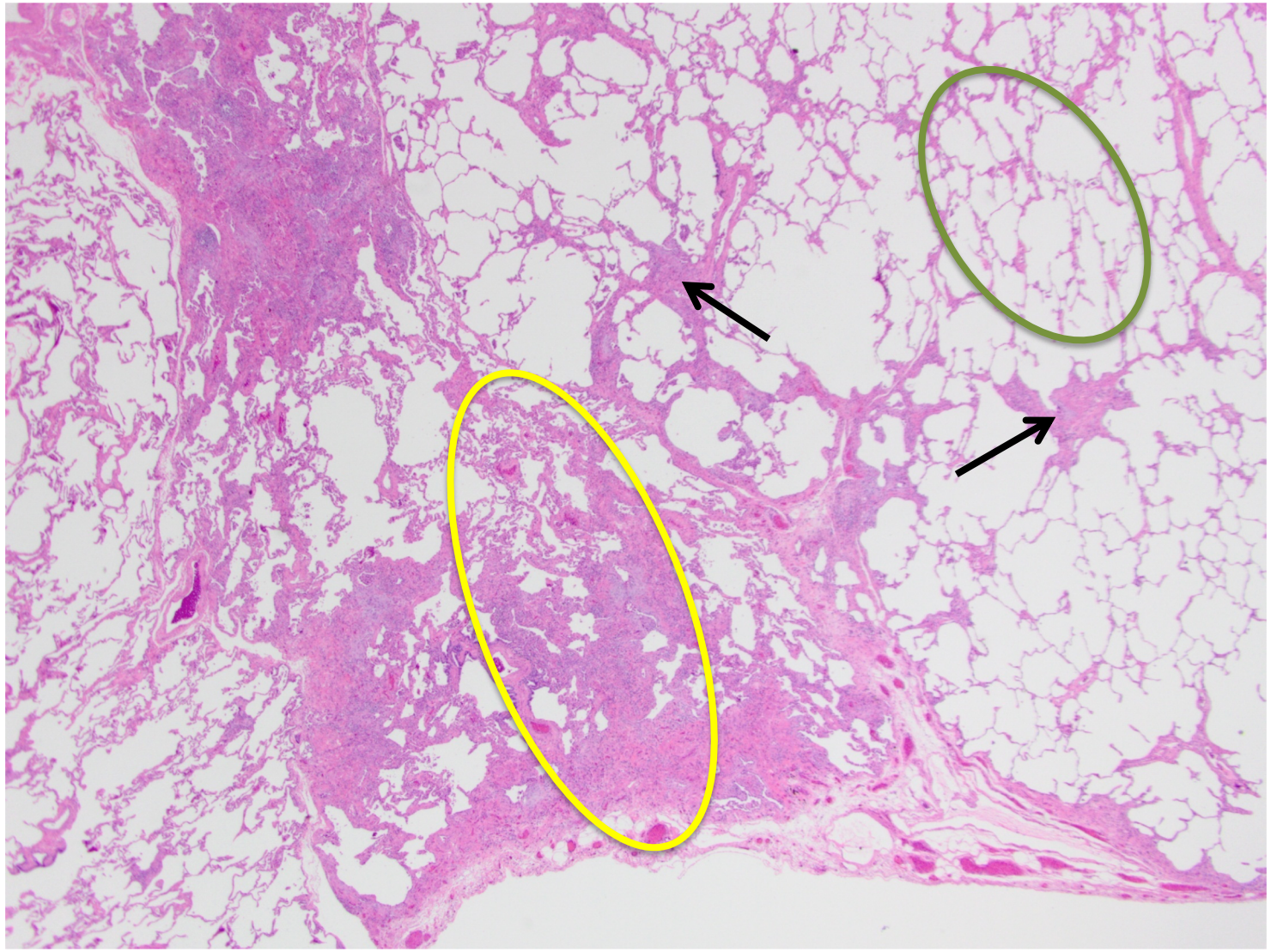
No Significant Benefit	Worse outcomes
Prednisone	Azathioprine + NAC + Prednisone
Imatinib	Ambrisentan
N-acetylcysteine	Coumadin
Bosentan	
Macitentan	
Sildenafil	
IFN-gamma	

Why were we failing to effectively treat this disease?

The progression of pulmonary fibrosis on CT imaging

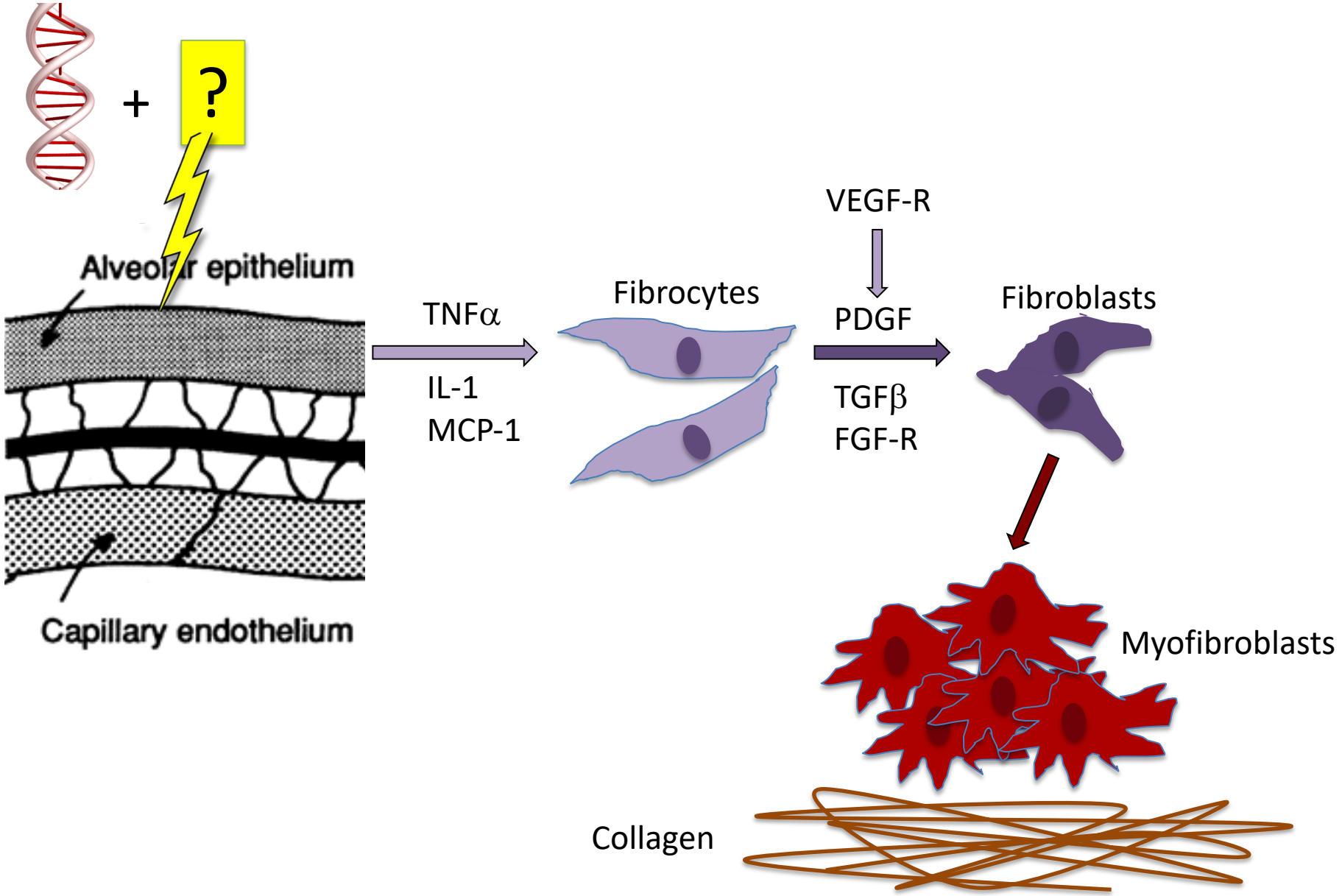


“Spatial heterogeneity and fibroblastic foci” constitute a pattern of UIP on biopsy



Courtesy of Paul Vanderlaan, MD

Pathogenesis



Pirfenidone—CAPACITY trials

Capacity 004 (72 weeks): 435 patients (174 high-dose; 87 low; 174 placebo)
FVC change: -8% vs -12.4% (p=0.001)
Change in 6MWT (m) -60.4 vs -76.8 (p=0.171)

Capacity 006 (72 weeks): 344 patients (171 high-dose; 173 placebo)
FVC change: -9% vs -9.6% (p=0.51)
Change in 6MWT (m) -45.1 vs -76.9 (p=0.0009)

Pooled data (72 weeks):
FVC change: -8.5% vs -11% (p=0.005)
Mortality
- All cause: 27 (8%) vs 34 (10%) p=0.315
- IPF-related: 18 (5%) vs 28 (8%) p=0.117

Lancet. 2011;377(9779):1760.

Pirfenidone (Esbriet)—ASCEND trial

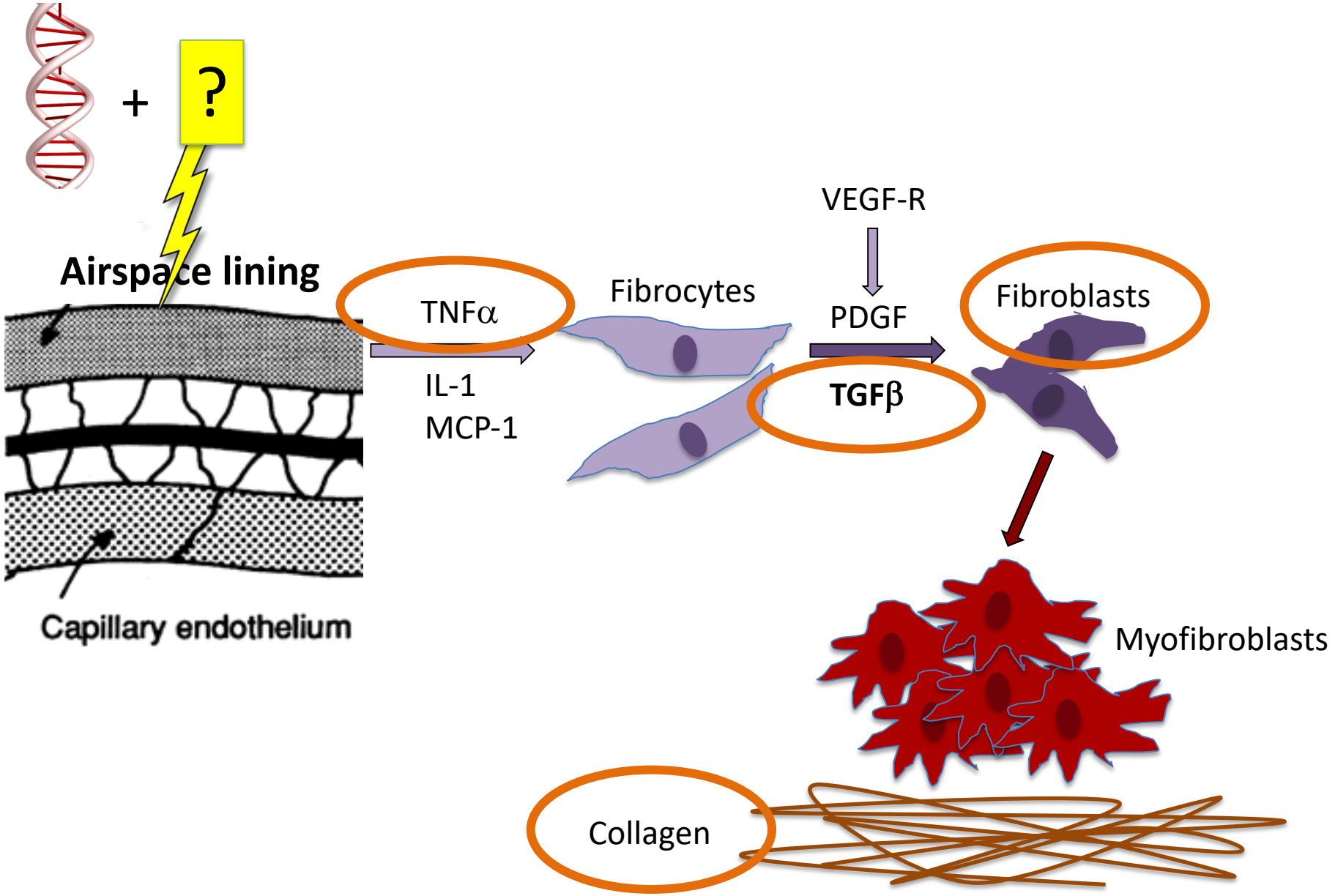
555 patients followed 52 weeks (278 high-dose; 277 placebo)
FVC 10% decline or death: 46 [16.5%] vs. 88 patients [31.8%]) p<0.001
FVC no decline: 63 patients [22.7%] vs. 27 patients [9.7%]) p=0.001

Mortality:
Overall: 11 (4%) vs 20 (7.2%) P = 0.10
IPF-related: 3 patients (1.1%) vs 7 patients (2.5%) P = 0.23

Pooled mortality (ASCEND + CAPACITY high-dose cut off at 52 weeks)
Overall: 22 (3.5%) vs 42 (6.7%) p=0.01
IPF-related: 7 (1.1%) vs 22.5 (3.5%) p=0.006

N Engl J Med. 2014;370(22):2083

Pirfenidone (Esbriet)



Nintedanib (Ofev)—INPULSIS trials

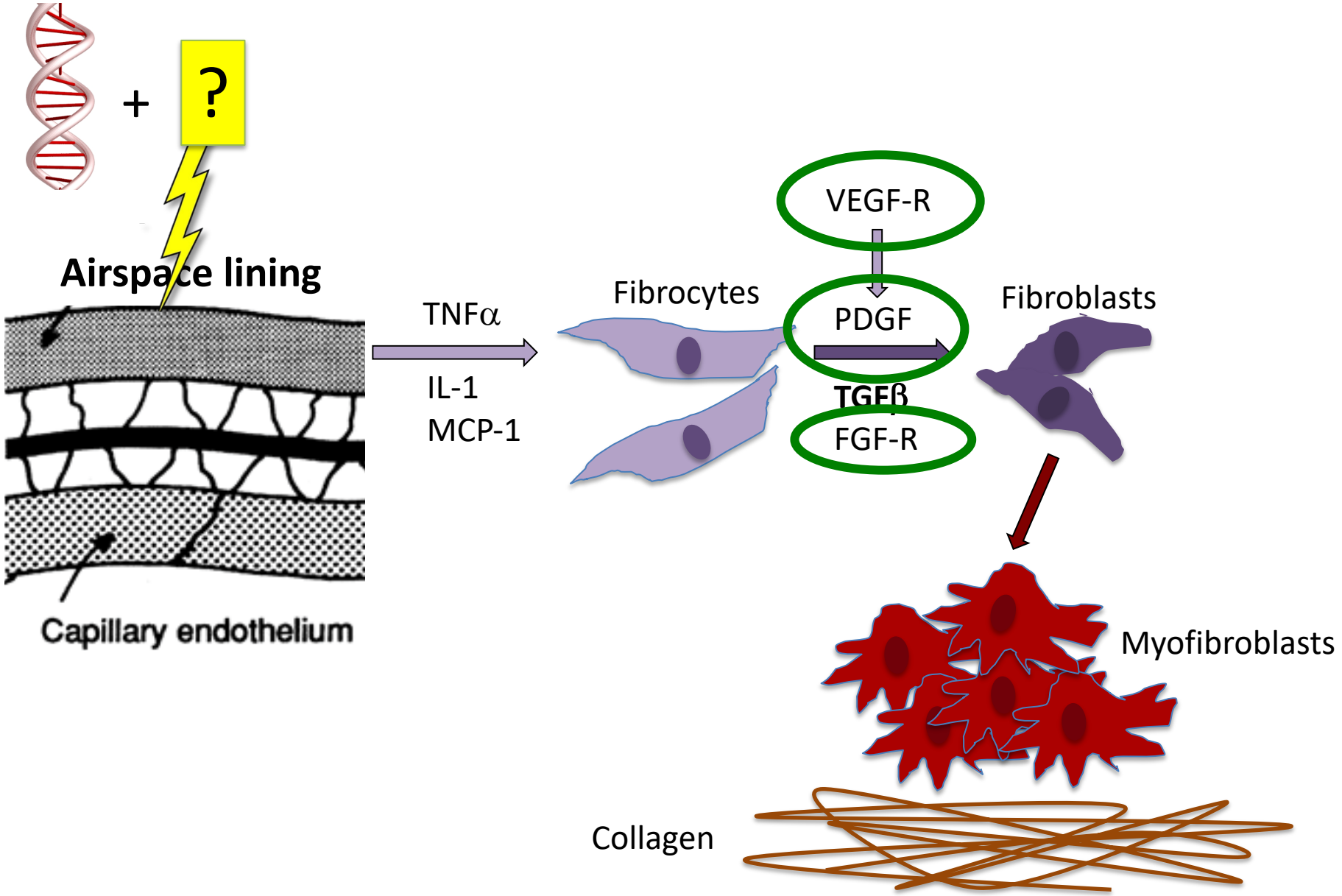
INPULSIS-1 (52 weeks) 513 patients (309 drug; 204 placebo)
FVC decline (52 weeks): −114.7 ml vs −239.9 (p<0.001)
Time to first exacerbation: HR 1.15 (P = 0.67)

INPULSIS-2 (52 weeks) 548 patients (329 drug; 219 placebo)
FVC deline (52 weeks): −113.6 ml vs −207.3 (p<0.001)
Time to first exacerbation: HR 0.38 (P = 0.005)

Pooled mortality from any cause:
5.5% vs 7.8%; HR 0.70 (P = 0.14)

N Engl J Med. 2014;370(22):2071

Nintedanib (Ofev)



Side Effects

Pirfenidone (Esbriet)

Nausea (36%)

Diarrhea (26%)

Abdominal pain (24%)

Photosensitivity (9%)

$110,000/yr

Nintedanib (Ofev)

Nausea (24%)

Diarrhea (62%)

Vomiting (12%)

$124,000/yr

N Engl J Med. 2014;370(22):2071
N Engl J Med. 2014;370(22):2083

Why not try combination therapy?

IPF involves dysregulation of multiple, complex pathways.

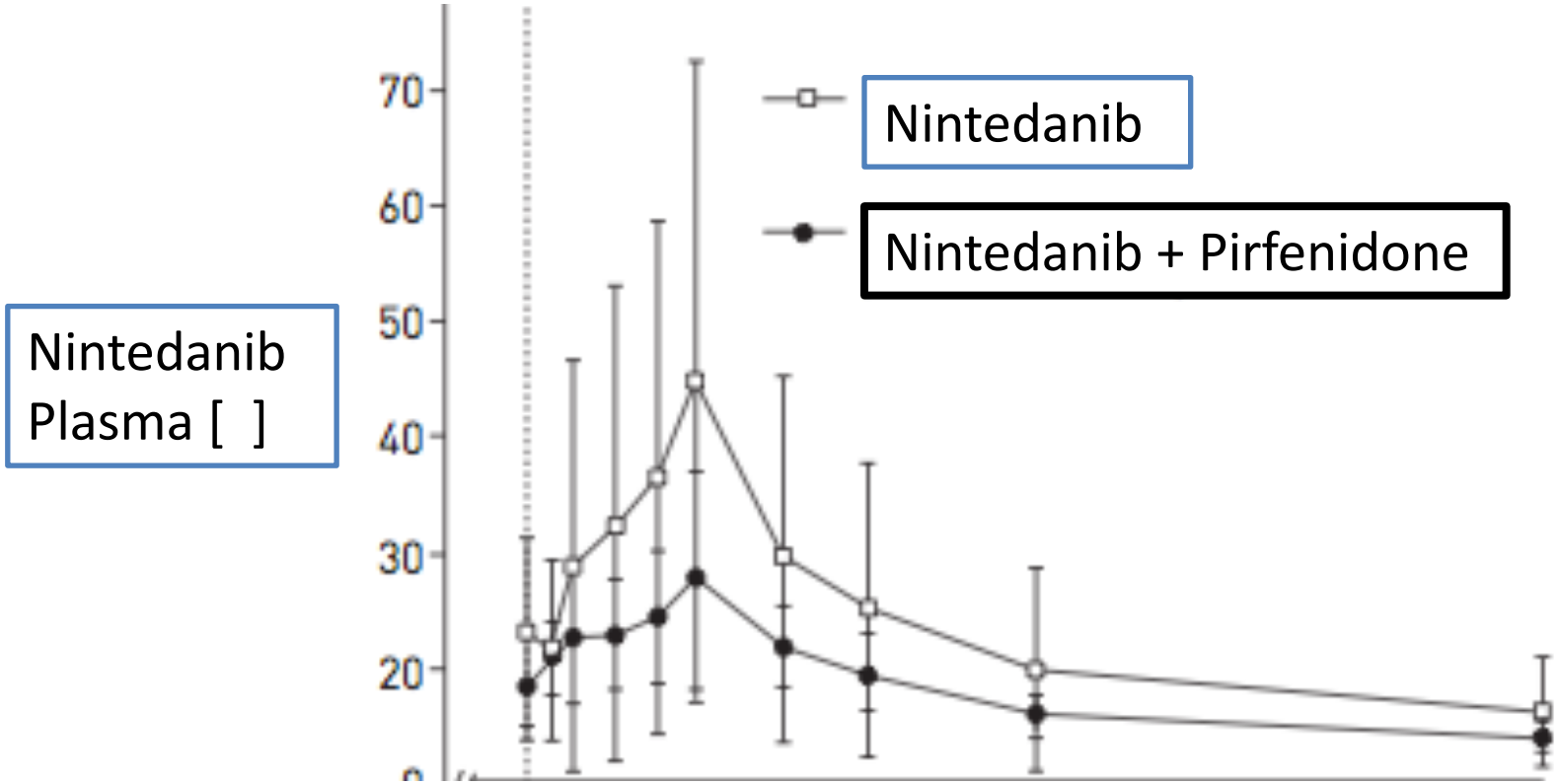
Barriers:

- Cost
- GI side effects
- Hard to show efficacy
- ? Pirfenidone decreases nintedinib levels

No biomarker to predict which agent is better

Pirfenidone *and* Nintedanib in combination

-- Perhaps more nausea or vomiting in the combination group
-- Pirfenidone lowers nintedanib levels?



Eur Respir J 2015; 45: 1382–1392

73 patients with nintedanib added to pirfenidone—combination was as well tolerated as each agent alone

TABLE 2 Summary of common treatment-emergent adverse events (TEAEs) and TEAEs leading to discontinuation (safety population[#])

	Patients with at least one TEAE[¶]	Patients with at least one TEAE related to pirfenidone only[+]	Patients with at least one TEAE related to nintedanib only[+]	Patients with at least one TEAE related to both pirfenidone and nintedanib[+]
TEAEs occurring in ⩾5% of patients				
⩾1 TEAE	88 (99)			
⩾1 treatment-related TEAE	74 (83)	15 (17)	67 (75)	26 (29)
Diarrhoea	44 (49)	2 (2)	38 (43)	5 (6)
Nausea	41 (46)	3 (3)	31 (35)	12 (14)
Vomiting	21 (24)	1 (1)	16 (18)	7 (8)
Decreased appetite	14 (16)	2 (2)	7 (8)	5 (6)
Fatigue	11 (12)	0	8 (9)	3 (3)
Dyspepsia	8 (9)	1 (1)	6 (7)	1 (1)
Headache	8 (9)	0	7 (8)	1 (1)
Weight decreased	6 (7)	1 (1)	3 (3)	2 (2)
Photosensitivity or rash TEAEs	7 (8)	4 (5)	2 (2)	1 (1)
Abdominal pain upper	5 (6)	1 (1)	2 (2)	2 (2)
Dizziness	5 (6)	0	4 (5)	1 (1)
TEAEs leading to discontinuation				
⩾1 TEAE	13 (15)			
⩾1 treatment-related TEAE	11 (12)	0	10 (11)	1 (1)
Nausea	4 (5)	0	3 (3)	1 (1)
Diarrhoea	4 (5)	0	3 (3)	1 (1)
Fatigue	2 (2)	0	2 (2)	0
Weight decreased	2 (2)	0	2 (2)	0
Deep vein thrombosis	1 (1)	0	1 (1)	0
Epigastric discomfort	1 (1)	0	1 (1)	0
Malaise	1 (1)	0	1 (1)	0
Migraine	1 (1)	0	1 (1)	0
Vomiting	1 (1)	0	1 (1)	0

Eur Respir J 2018; 52: 1800230

Nintedanib with Add-on Pirfenidone in Idiopathic Pulmonary Fibrosis

Results of the INJOURNEY Trial

Carlo Vancheri[1], Michael Kreuter[2], Luca Richeldi[3], Christopher J. Ryerson[4], Dominique Valeyre[5], Jan C. Grutters[6,7], Sabrina Wiebe[8], Wibke Stansen[9], Manuel Quaresma[2,9], Susanne Stowasser[9], and Wim A. Wuyts[10]; on behalf of the INJOURNEY Trial Investigators

51 Nintedanib alone; 53 combination

	Nintedanib 150 mg Twice Daily with Add-on Pirfenidone (*n* = 53)	Nintedanib 150 mg Twice Daily (*n* = 51)
Any adverse events	47 (88.7)	45 (88.2)
Most frequent adverse events*		
Diarrhea	20 (37.7)	16 (31.4)
Nausea	22 (41.5)	6 (11.8)
Vomiting	15 (28.3)	6 (11.8)
Fatigue	10 (18.9)	6 (11.8)
Upper abdominal pain	7 (13.2)	4 (7.8)
Decreased appetite	6 (11.3)	5 (9.8)
Dyspnea	2 (3.8)	8 (15.7)
Headache	7 (13.2)	1 (2.0)
Any serious adverse events†	2 (3.8)	5 (9.8)
Any fatal adverse events	0	0

Am J Respir Crit Care Med Vol 197, Iss 3, pp 356–363, Feb 1, 2018

The role of lysophosphatidic acid (LPA) and autotaxin in pulmonary fibrosis

Bleomycin mouse model:

- Increased LPA levels following lung injury
- Mice lacking the LPA1 receptor are protected from fibrosis and mortality
  --Less fibroblast recruitment and vascular leak
- Increased autotaxin expression following bleomycin injury
- Mice whose lung epithelium can't produce autotaxin have fibrotic damage following bleomycin

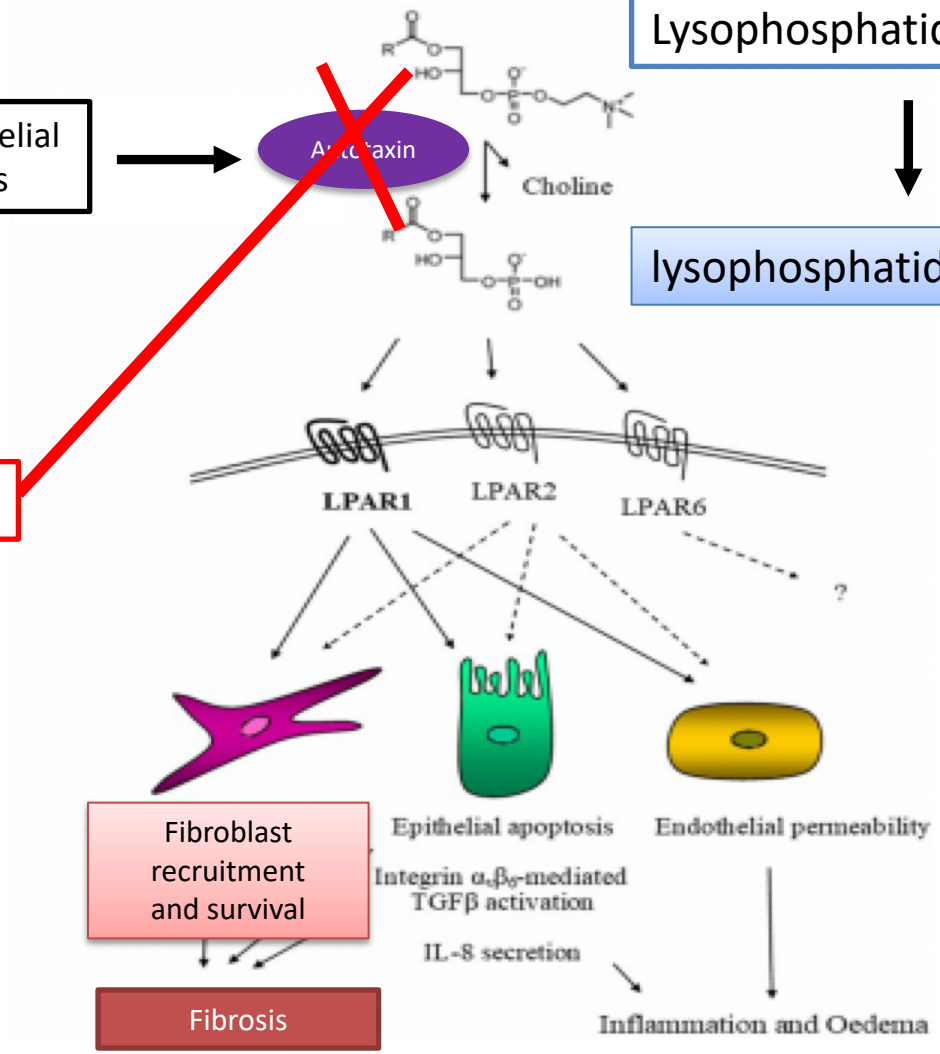
In humans with IPF:

- Elevated levels of LPA in lung lavage fluid of IPF patients
- Inhibiting the LPA1 receptor in a test tube reduced fibroblast activity
- Increased expression of autotaxin in the lung tissue of patients with lung fibrosis

Tager et al. Nature Med. Vol 14 (1) Jan 2008
Oikonomou et al. Am J Respir Cell Mol Biol Vol 47, Iss. 5, pp 566–574, Nov 2012

Lysophosphatidylcholine (LPC)

Pulmonary epithelial macrophages



lysophosphatidic acid (LPA)

GLPG1690

Fibroblast recruitment and survival

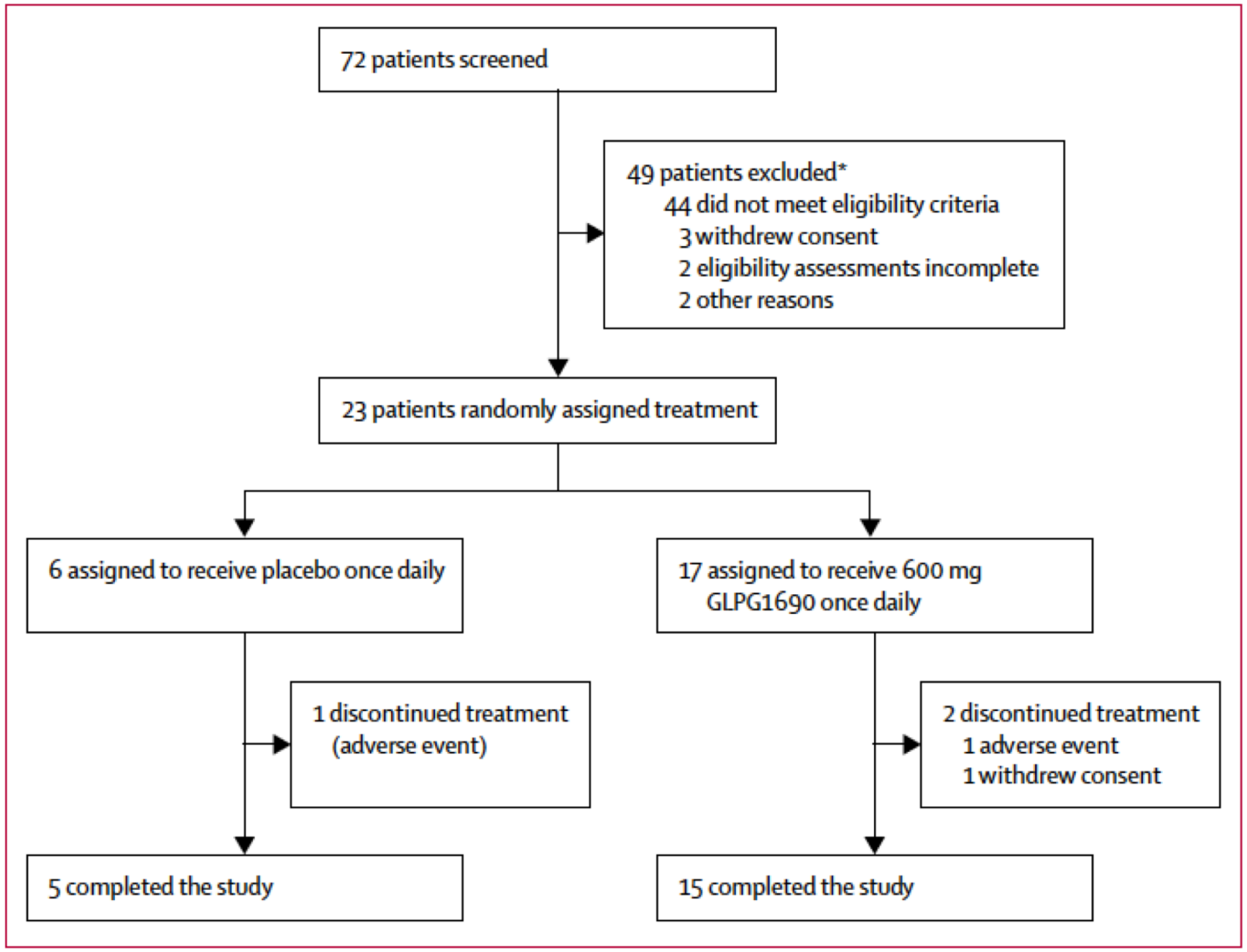
Fibrosis

Galápagos

GLPG1690: selective autotaxin inhibitor

Front Med (Lausanne). 2018; 5: 180.

Safety, tolerability, pharmacokinetics, and pharmacodynamics of **GLPG1690**, a novel autotaxin inhibitor, to treat idiopathic pulmonary fibrosis (FLORA): a phase 2a randomized placebo-controlled trial

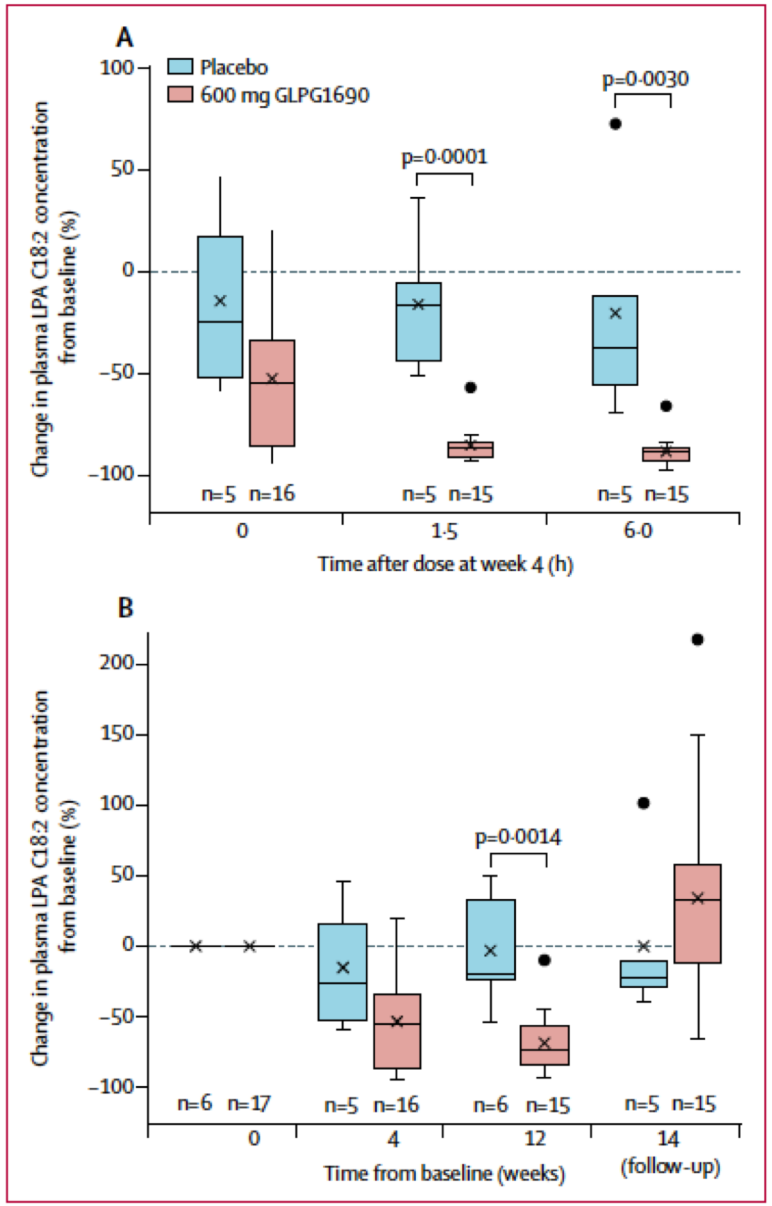


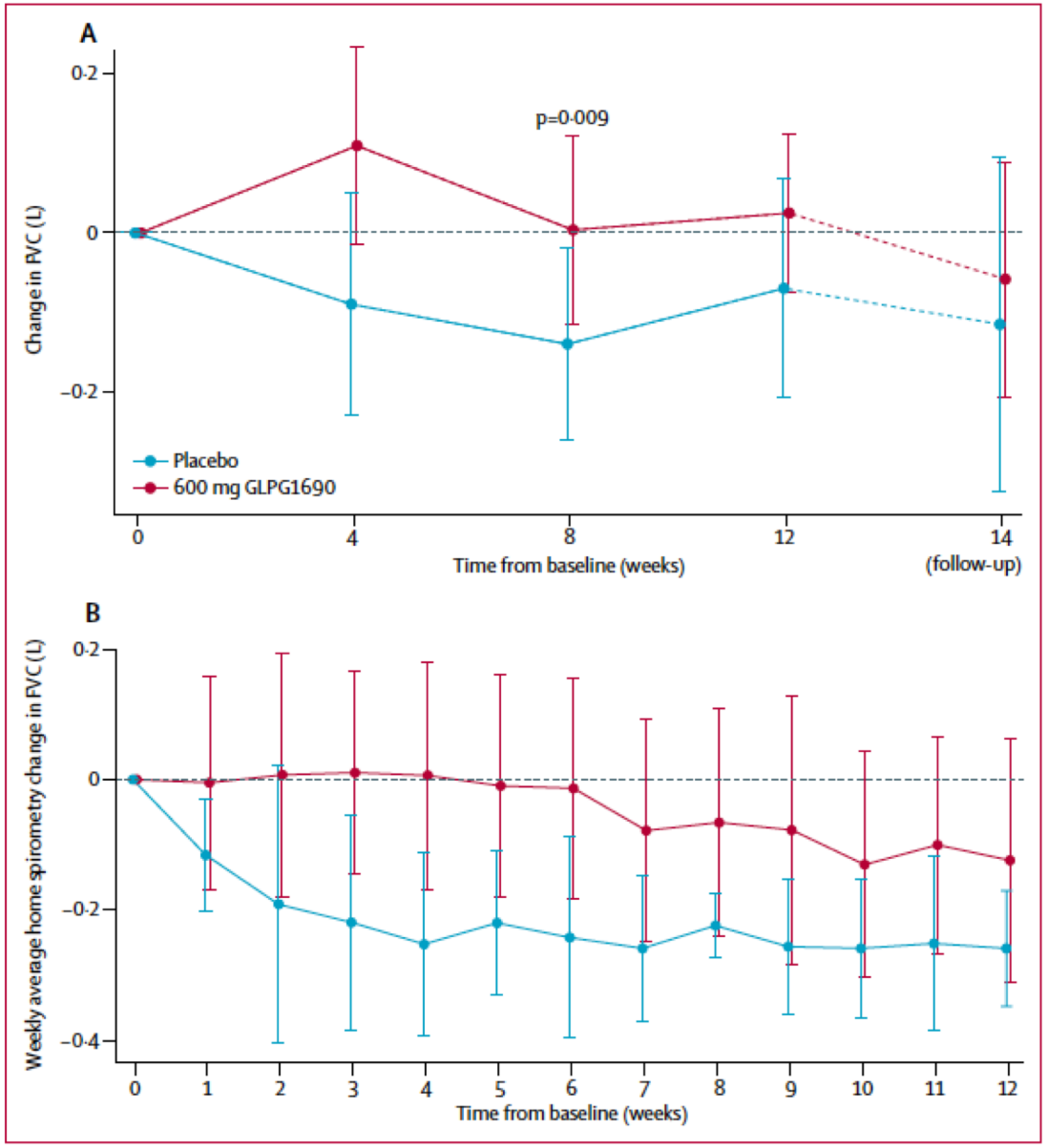
Maher et al. Lancet Respir Med 2018;6: 627–35

Results from FLORA, the phase 2 study of **GLPG1690**, an autotaxin inhibitor

Change in blood LPA concentration

Change in blood LPA concentration





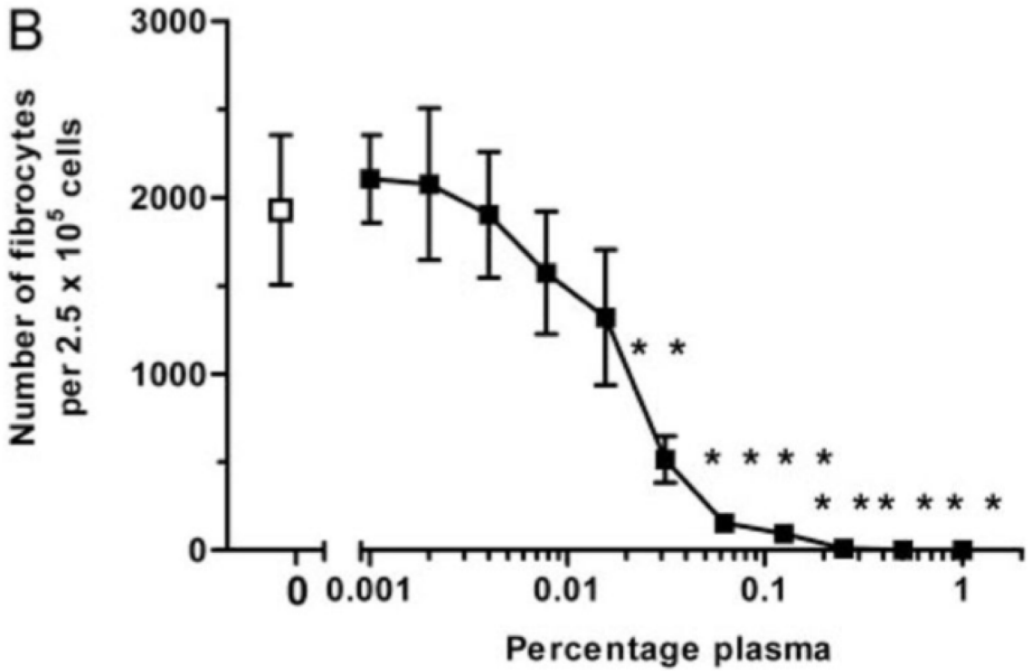
Maher et al. Lancet Respir Med 2018;6: 627–35

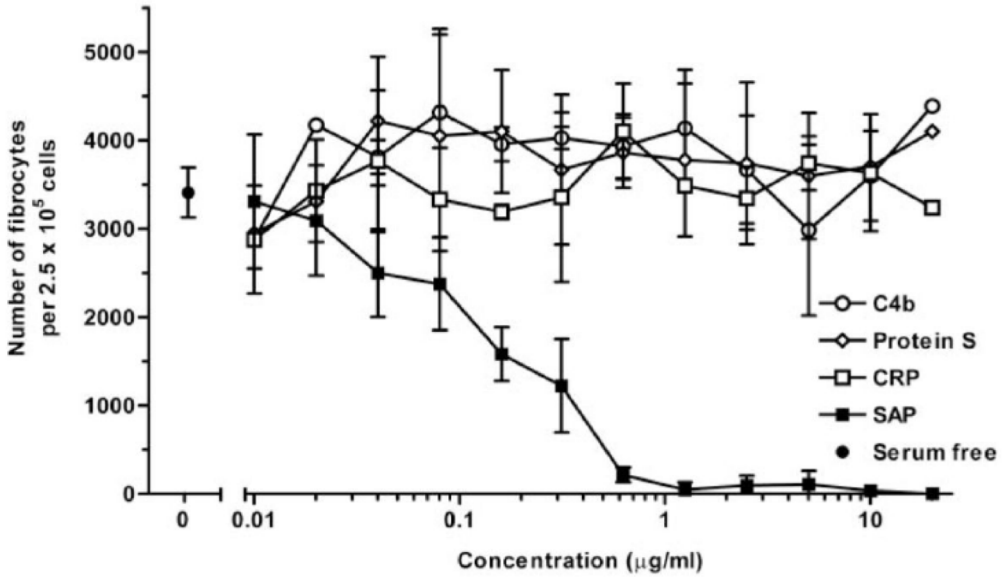
ISABELA2: A Phase 3, Randomized, Double-blind, Parallel-group, Placebo-controlled, Multi-center Study to Evaluate the Efficacy and Safety of Two Doses of **GLPG1690** in Addition to Local Standard of Care for Minimum 52 Weeks in Subjects With Idiopathic Pulmonary Fibrosis. NCT03733444

Clinical Trials Number NCT03733444
132 locations
Target enrollment: 750 patients

Galápagos

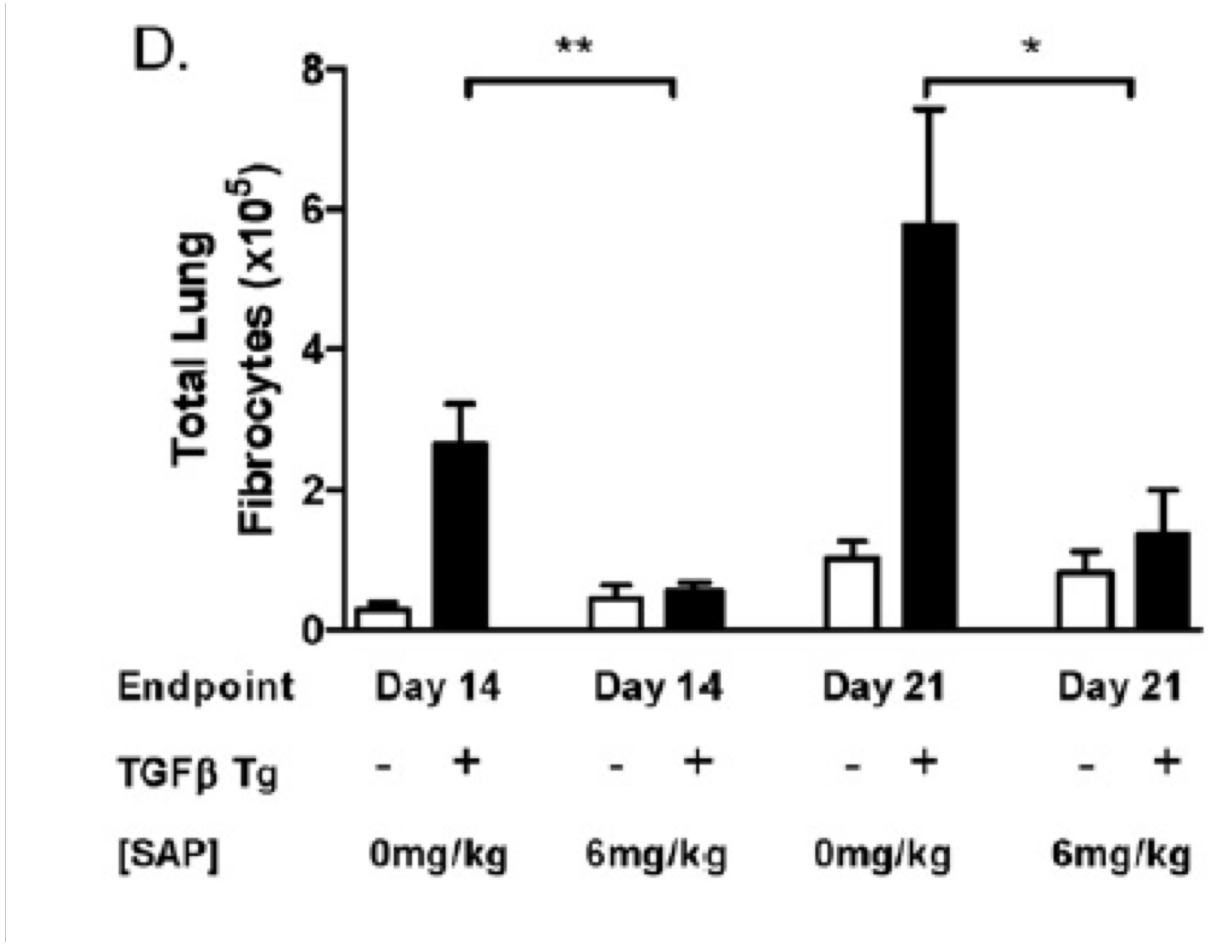
Pentraxin 2 (serum amyloid P) inhibits fibrocytes





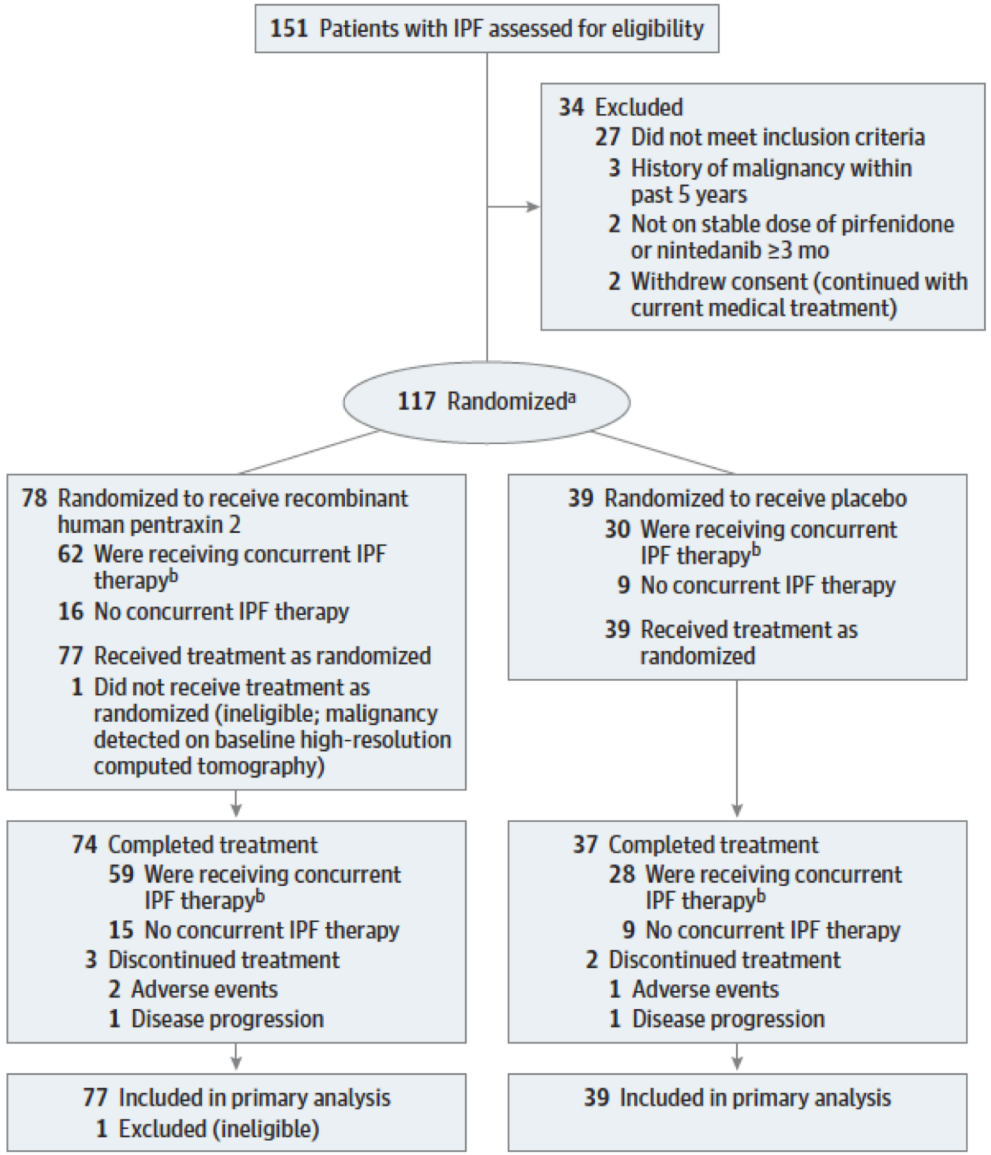
Pilling et al. *J Immunol*. 2003 November 15; 171(10): 5537–5546.

Pentraxin-2 inhibits TGFβ–induced fibrocyte activation in a mouse model



Murray et al. Int J Biochem & Cell Bio 43 (2011) 154–162

Figure 1. Participant Flow in a Trial of Recombinant Human Pentraxin 2 vs Placebo for Idiopathic Pulmonary Fibrosis



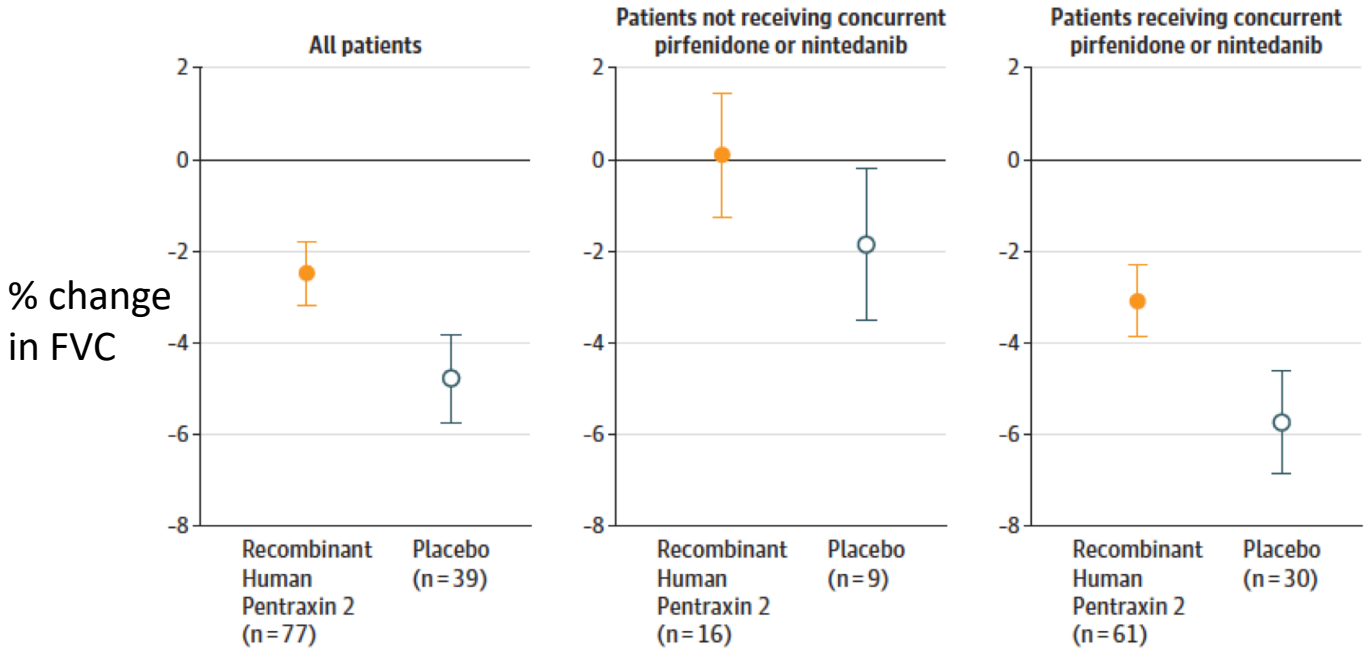
PROMOTE

Promedior Evaluation of PRM-151

(Pentraxin-2)

-Phase II study of 117 patients
-Placebo vs PRM-151
-Treated for 28 weeks

Raghu et al. JAMA. 2018;319(22):2299-2307

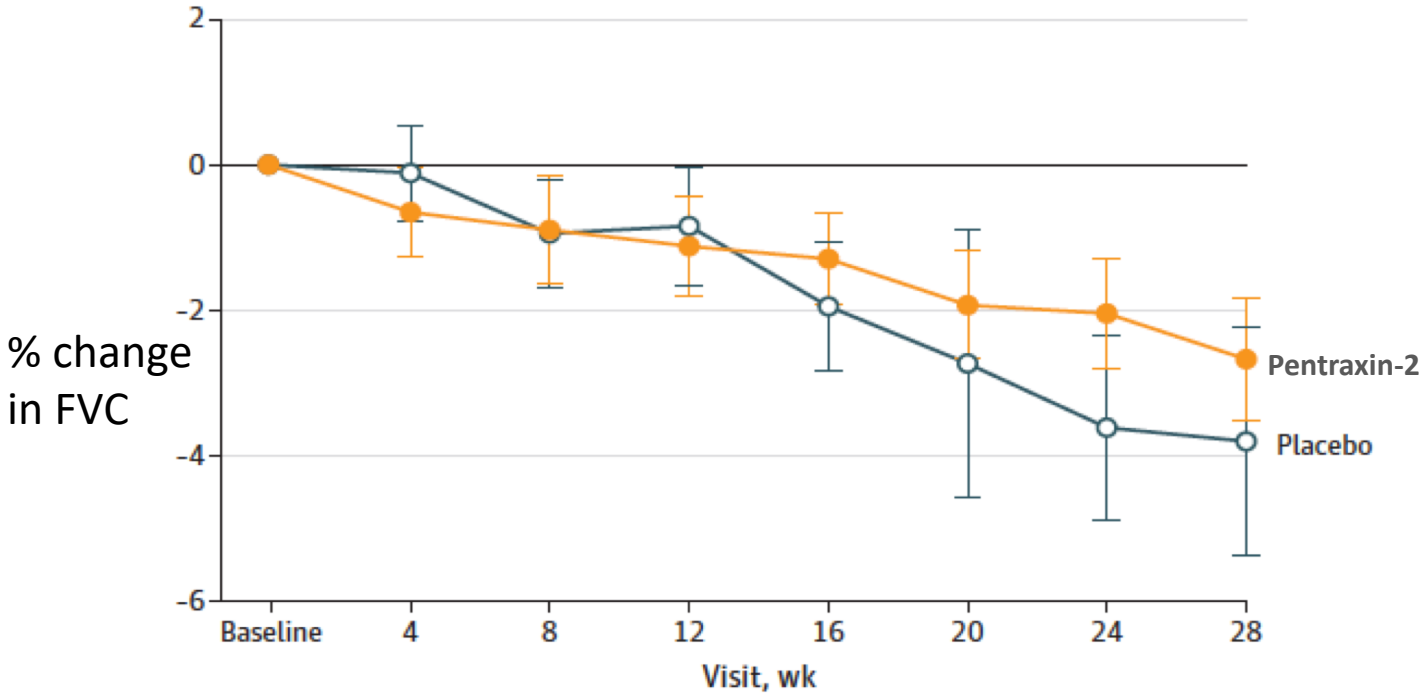


PROMOTE

Promedior Evaluation of PRM-151

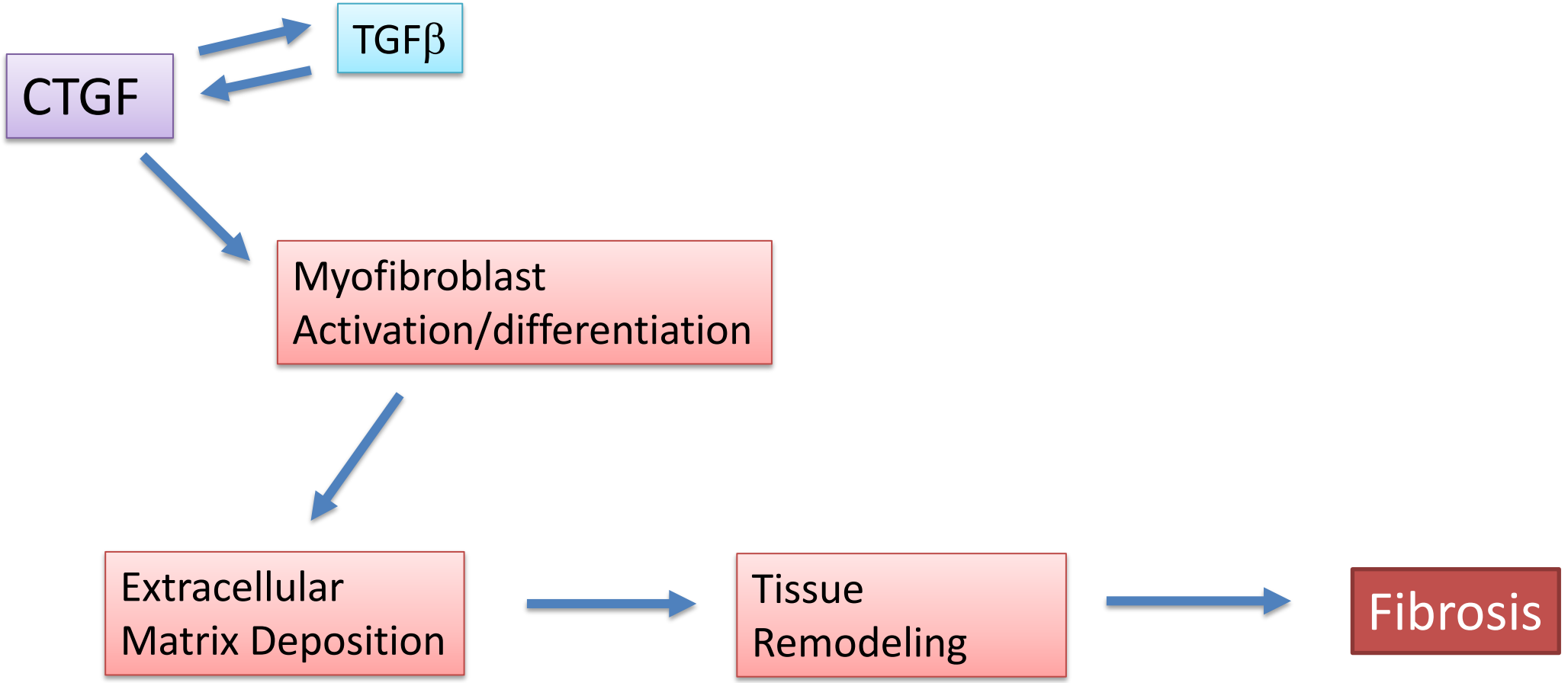
FVC decline: -2.5% vs -4.8% (p =.001)

6MWD change −0.5 m vs −31.8 m (p < .001)



Raghu et al. JAMA. 2018;319(22):2299-2307

The role of connective tissue growth factor (CTGF) in pulmonary fibrosis



Lipson et al. *Fibrogenesis & Tissue Repair* 2012, 5(Suppl 1):S24

CTGF messenger RNA expression is significantly enhanced in the lung lavage fluid from patients with IPF

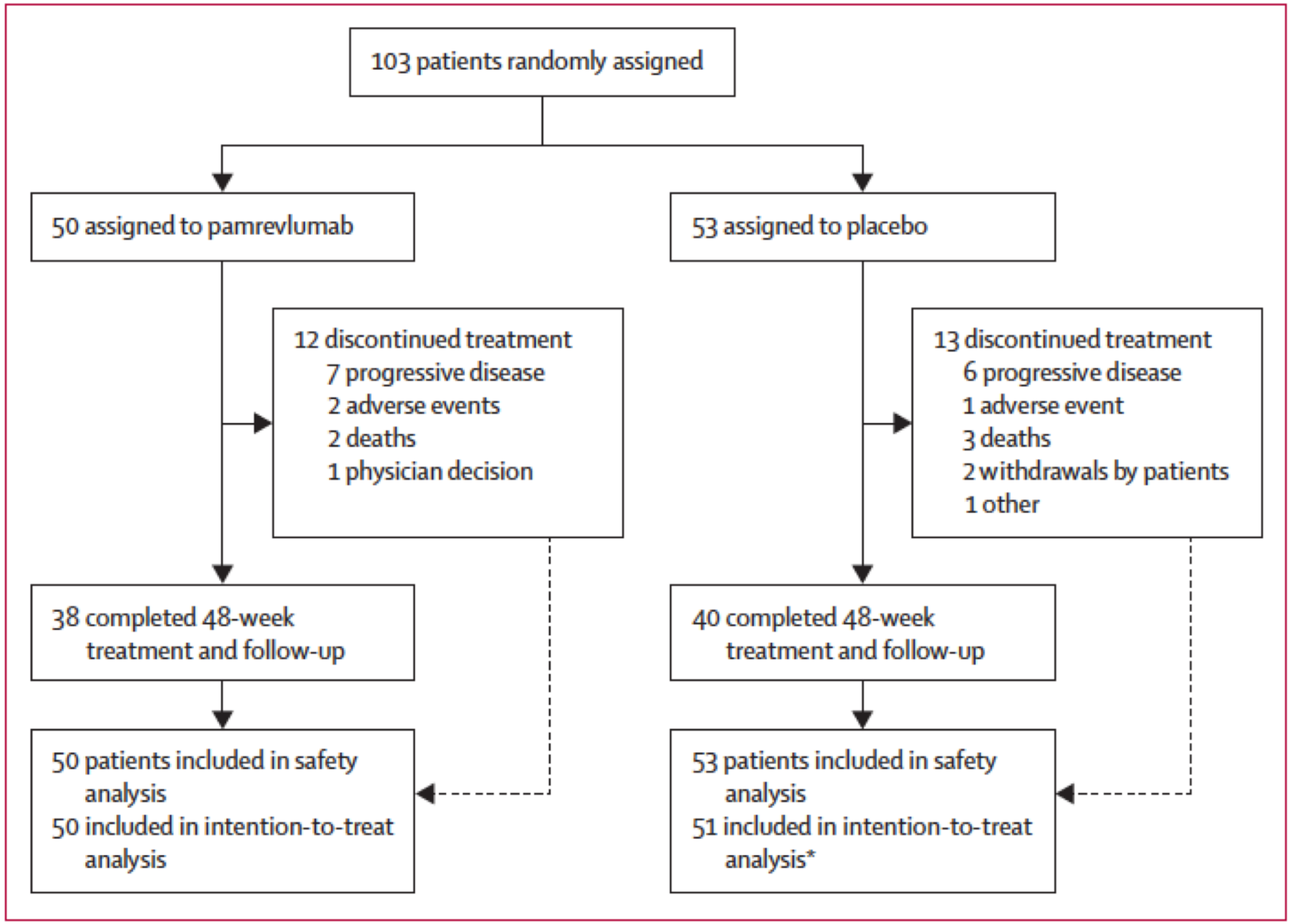
TABLE 3

Summary of IGFBP-rP2 gene expression

Subject Group (*n*)	mRNA Transcripts/10^6 G3PDH Molecules*
Normal (7)	512 (± 97)
IPF (18)	5,455 (± 2,560)
Sarcoid [I + II] (8)	20,932 (± 11,714)
Sarcoid [III + IV] (5)	47,910 (± 24,505)

*Mean (± standard error of the mean).

Allen et al. Am. J. Respir. Cell Mol. Biol. 21:693–700.



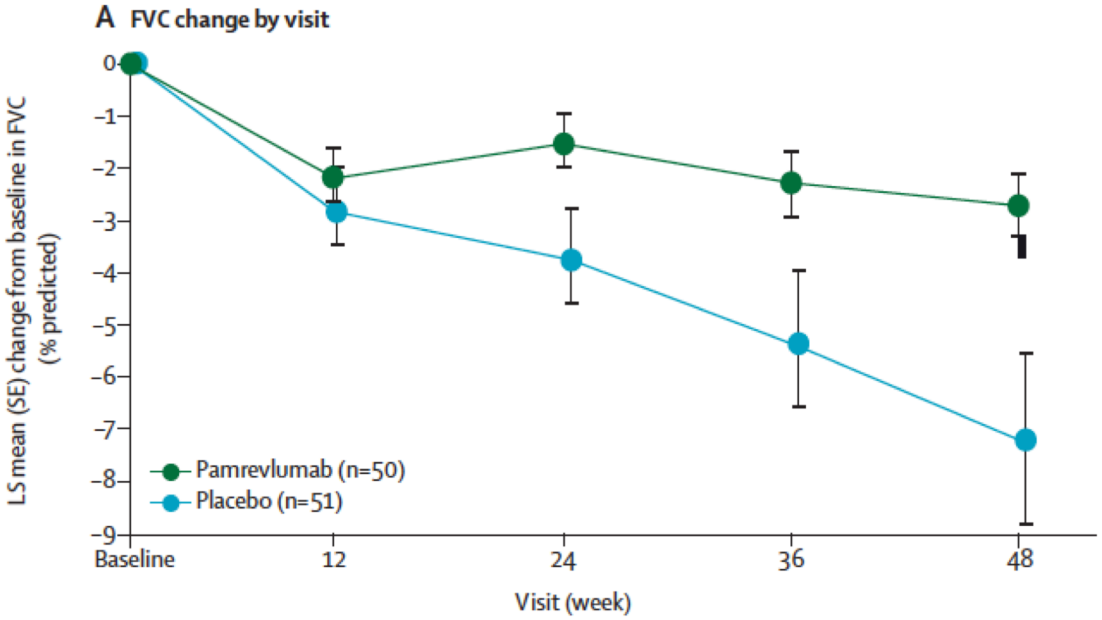
FibroGen

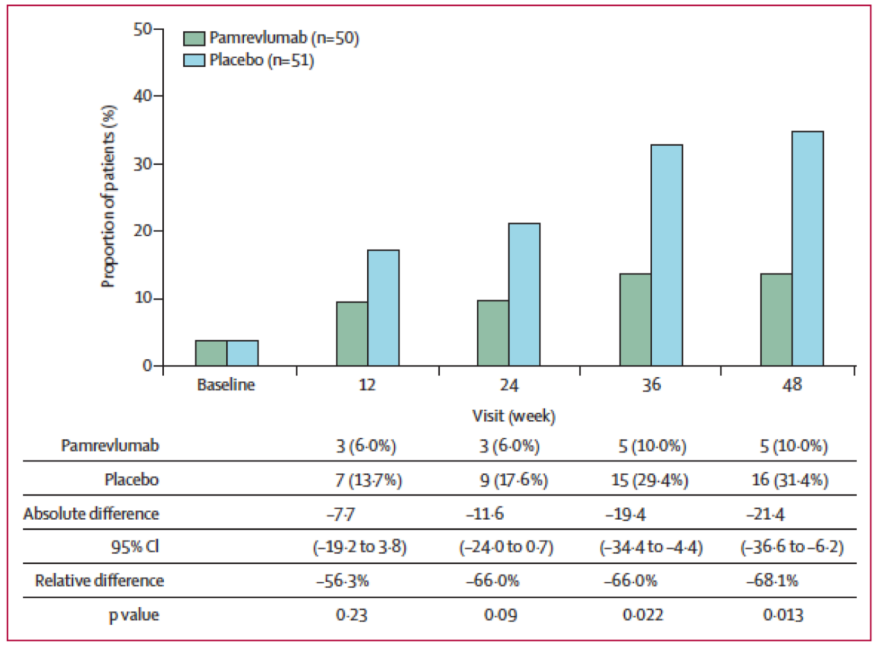
Pamrevlumab—monoclonal antibody that inhibits connective tissue growth Factor (CTGF).

Phase 2 study

Richeldi et al. Lancet Respir Med 2020;8: 25–33

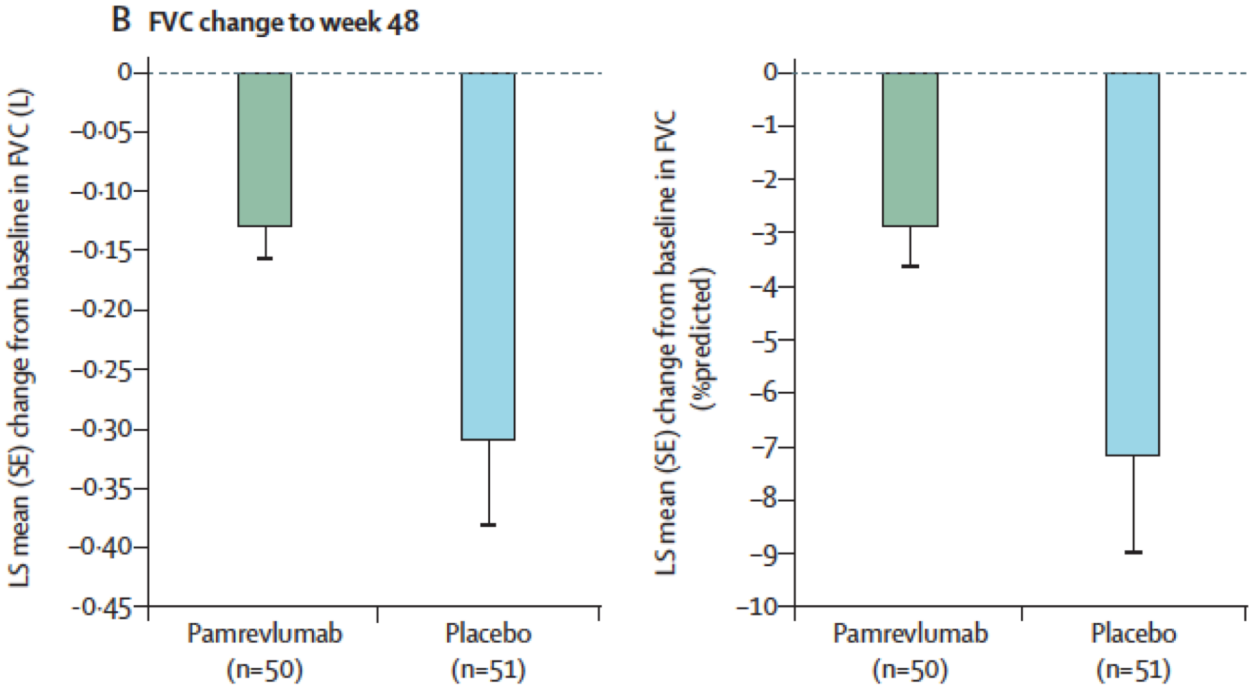
Pamrevlumab appears to slow the progression of IPF





	Baseline	12	24	36	48
Pamrevlumab		3 (6·0%)	3 (6·0%)	5 (10·0%)	5 (10·0%)
Placebo		7 (13·7%)	9 (17·6%)	15 (29·4%)	16 (31·4%)
Absolute difference		−7·7	−11·6	−19·4	−21·4
95% CI		(−19·2 to 3·8)	(−24·0 to 0·7)	(−34·4 to −4·4)	(−36·6 to −6·2)
Relative difference		−56·3%	−66·0%	−66·0%	−68·1%
p value		0·23	0·09	0·022	0·013

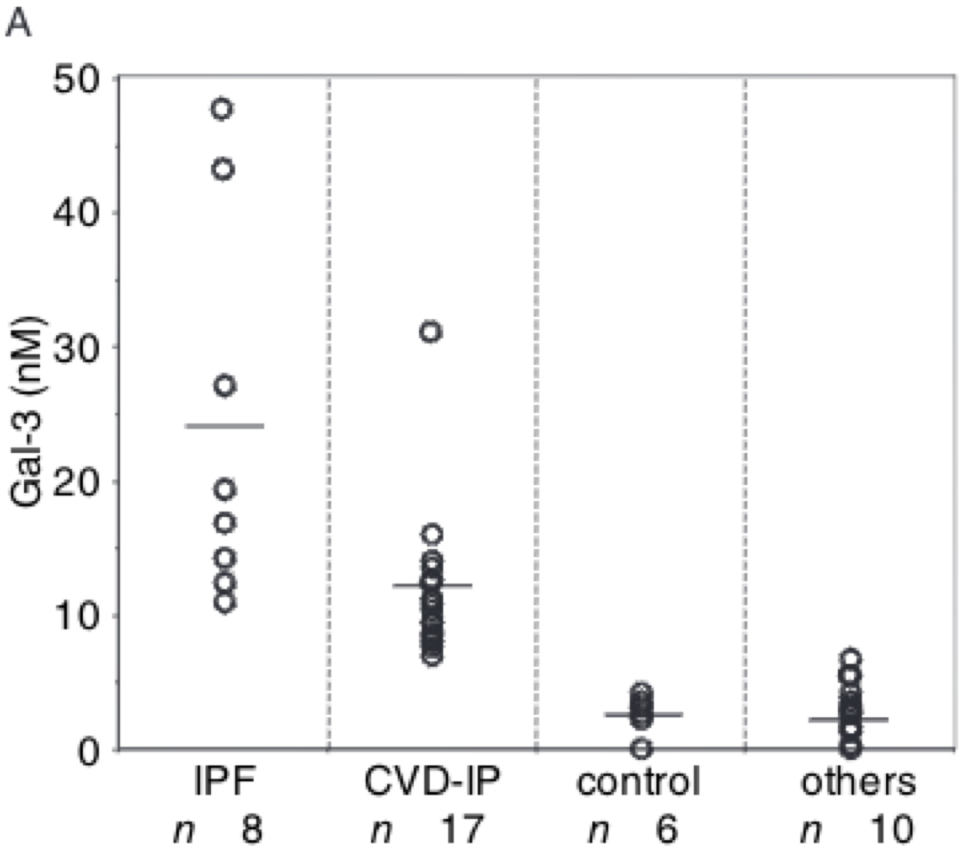
Figure 3: **Proportion of patients with decline in percentage of predicted FVC of 10% or greater, or death, by visit**

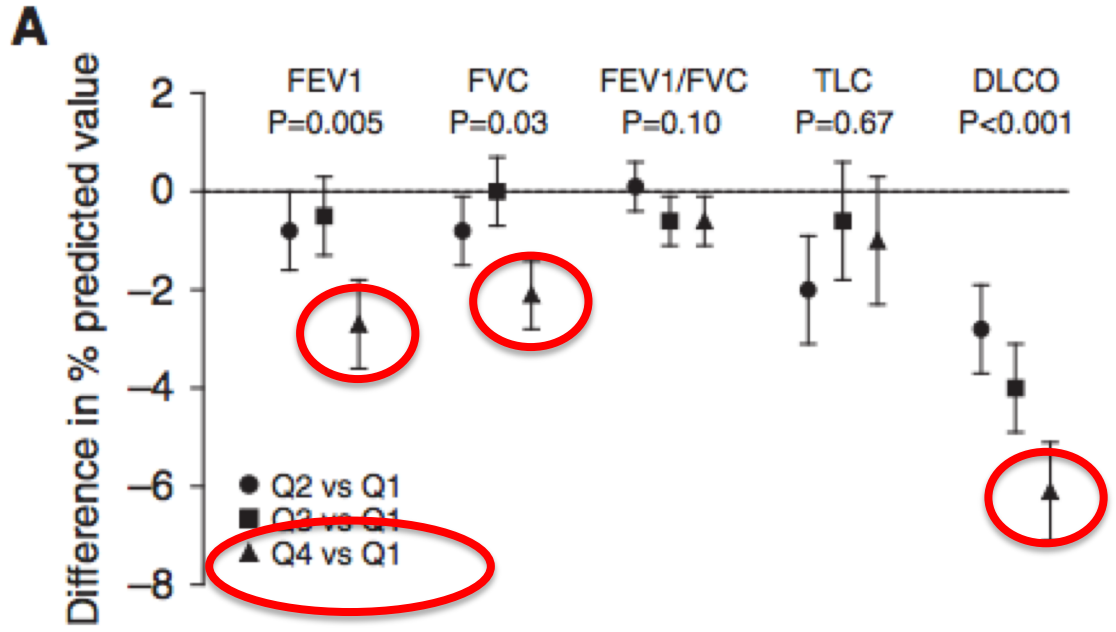


*A Phase 3 study is now ongoing

Richeldi et al. Lancet Respir Med 2020;8: 25–33

Elevated Galectin-3 levels are associated with ILD





Q4 Gal-3 had an OR of 2.67 to have interstitial lung abnormalities (95% CI, 1.49–4.76; P=0.001).

Nishi et al. *Allergology International.* 2007;56:57-65
Ho et al. Am J Respir Crit Care Med Vol 194, Iss 1, pp 77–83, Jul 1, 2016

A Study to Test the Efficacy and Safety of Inhaled TD139 in Subjects With IPF (GALACTIC-1)

Clinical trials number NCT03832946

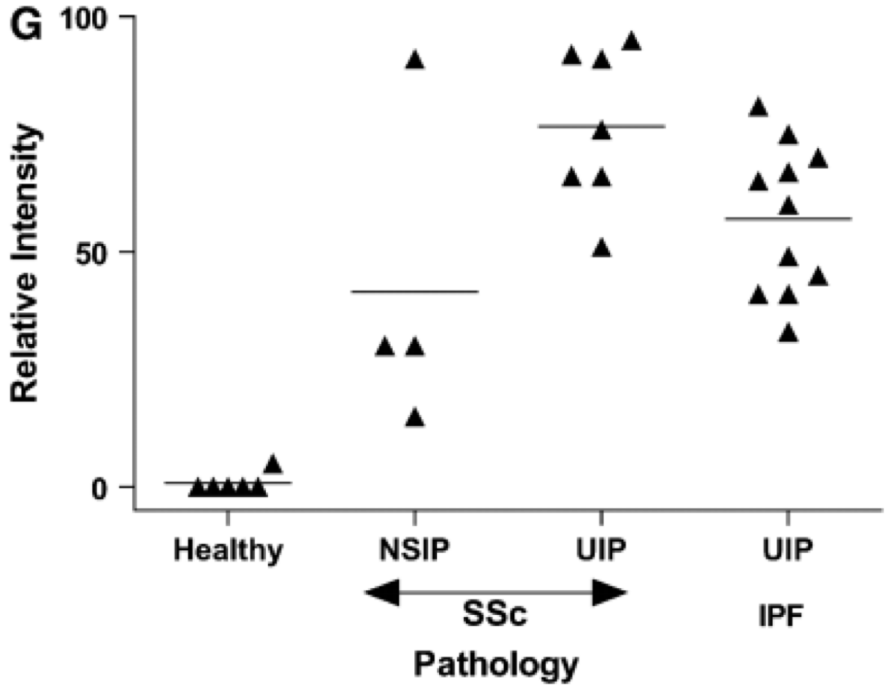
TD139

- Galectin-3 inhibitor (dry powder)
- 450 patients over 52 weeks

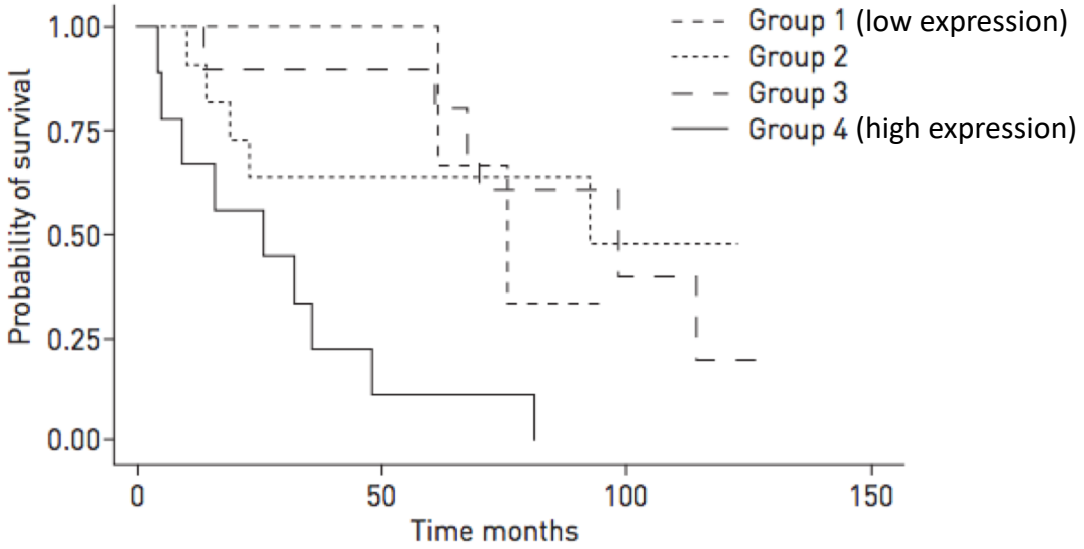
Galecto

αvβ6 expression is associated with fibrotic ILD

αvβ6 expression in different disease states

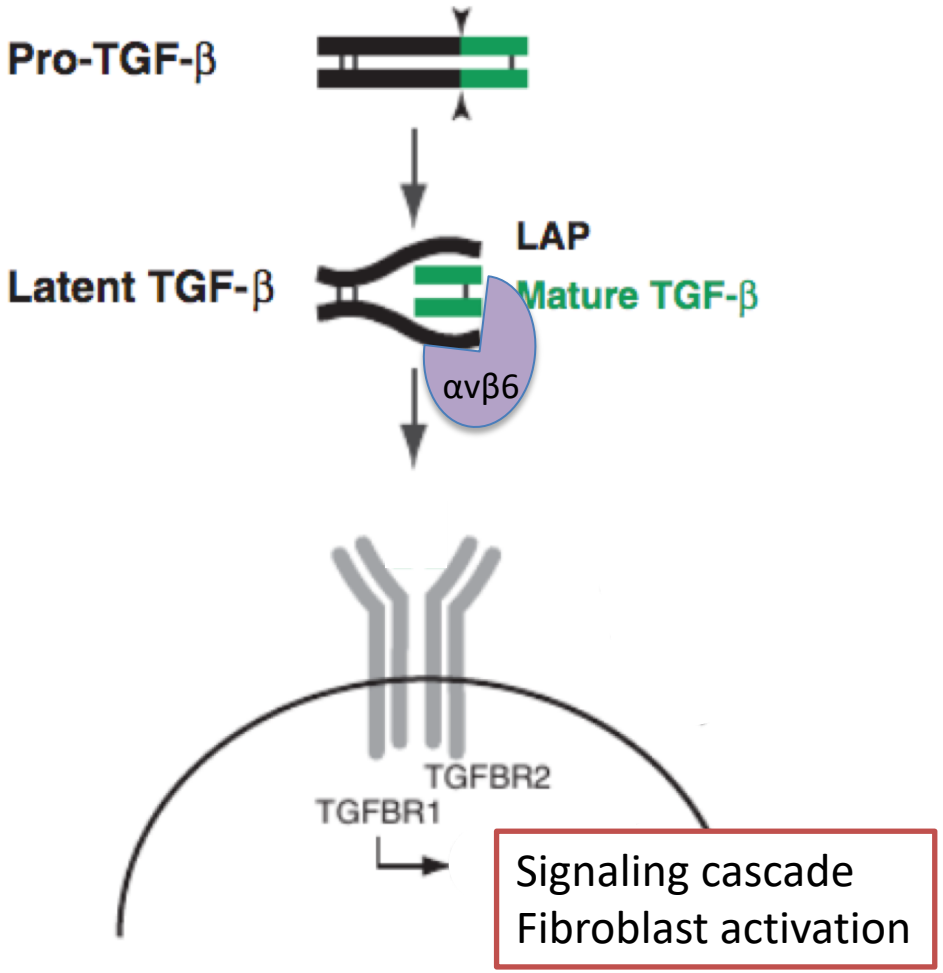


Survival based on level of αvβ6 expression in lung biopsy tissue



Horan et al. Am J Respir Crit Care Med Vol 177. pp 56–65, 2008
Saini et al. Eur Respir J 2015; 46: 486–494

How does **αvβ6** contribute to pulmonary fibrosis?

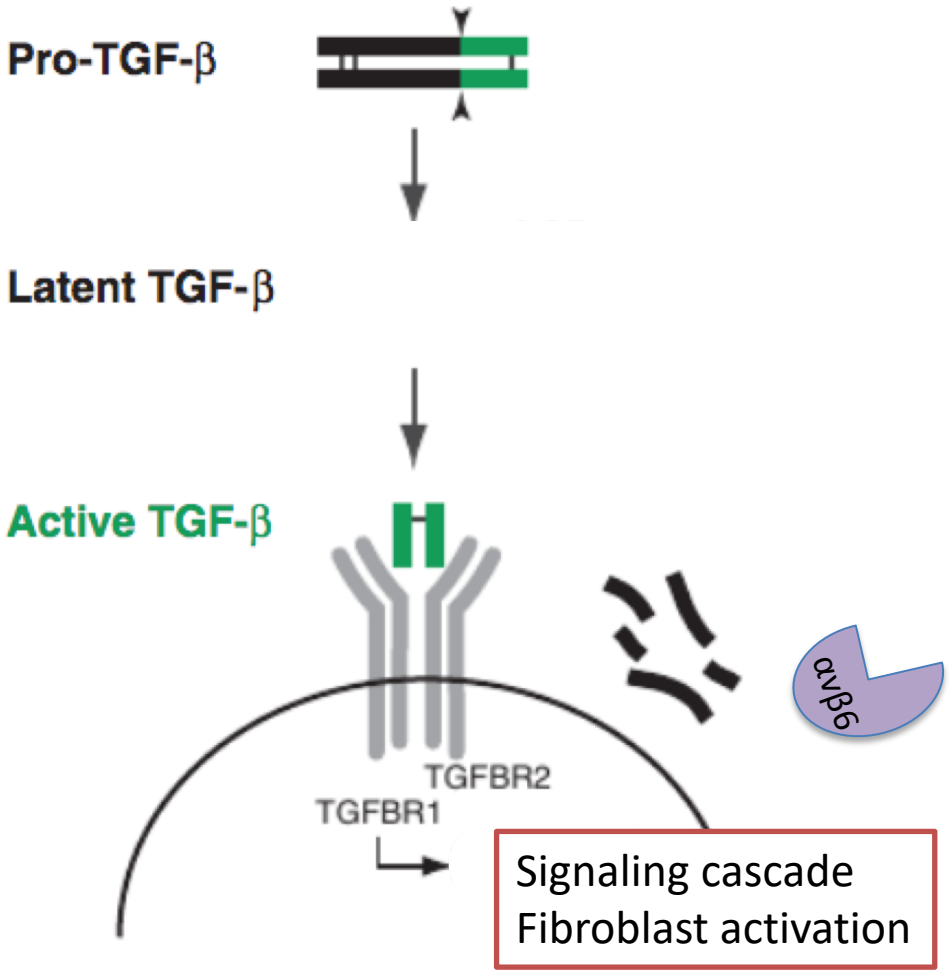


- TGF-β is secreted in a latent form and coupled with latency-associated protein (LAP).
- αvβ6 binds to LAP, releasing TGF-β so that it is activated and free to bind to its receptor
- Mice lacking αvβ6 are protected from lung fibrosis in a bleomycin model

Figure adapted from Stockis et al. *Eur. J. Immunol*. 2009. 39: 3315–3322

Munger et al. *Cell*. Vol. 96, 319–328, February 5, 1999

How does αvβ6 contribute to pulmonary fibrosis?



- TGF-β is secreted in a latent form and coupled with latency-associated protein (LAP).
- αvβ6 binds to LAP, releasing TGF-β so that it is activated and free to bind to its receptor
- Mice lacking αvβ6 are protected from lung fibrosis in a bleomycin model

Figure adapted from Stockis et al. *Eur. J. Immunol*. 2009. 39: 3315–3322

Munger et al. *Cell*. Vol. 96, 319–328, February 5, 1999

An Efficacy and Safety Study of *BG00011* in Participants With Idiopathic Pulmonary Fibrosis (SPIRIT)

Clinical trials number NCT03573505

A Randomized, Double-Blind, Placebo-Controlled Study (phase 2) with 109 participants

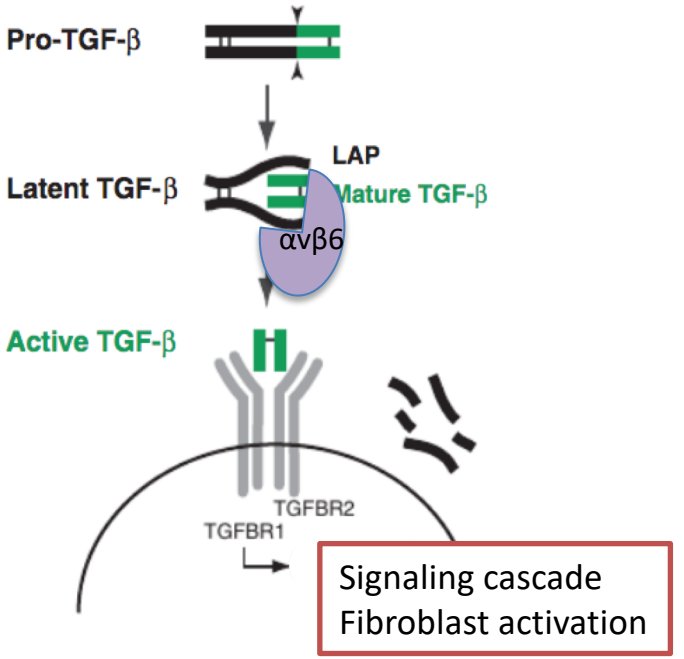
BG00011 = humanized anti-αvβ6 monoclonal antibody

Study was terminated due to safety concerns

A Phase 2a, multicenter, 3-part, randomized, double-blind, dose-ranging, placebo-controlled study to evaluate the safety, tolerability, and PK of once-daily treatment with **PLN-74809** in participants with idiopathic pulmonary fibrosis.

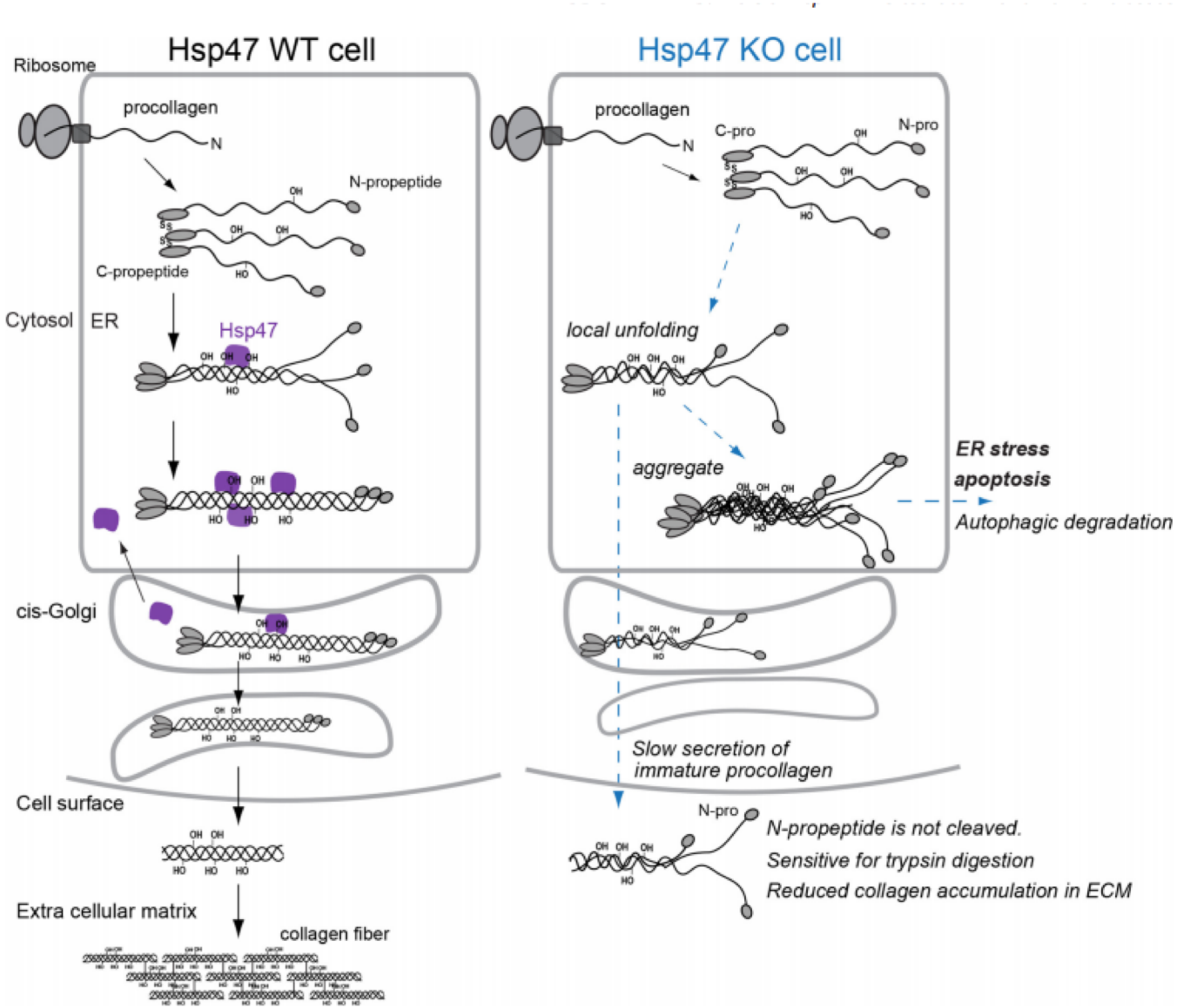
Clinical trials number NCT04396756
84 patients

PLN-74809 is an inhibitor of αvβ1 / αvβ6



PLIANT

The role of Hsp47 in collagen synthesis



Ito et al. J. Biol. Chem. (2019) 294(6) 2133–2141

JUNIPER: A Phase 2 Study to Evaluate the Safety, Biological Activity, and PK of **ND-L02-s0201** in Subjects With IPF

Clinical trials number NCT03538301

ND-L02-s0201 is a targeted siRNA therapy that is designed to inhibit Hsp47

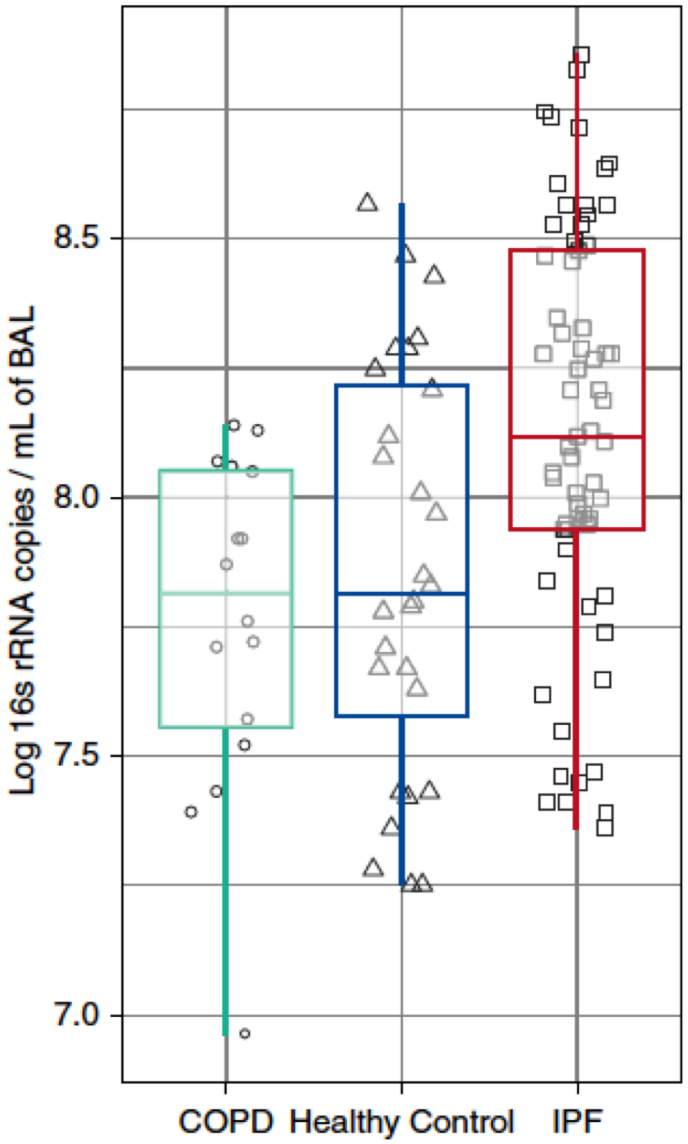
120 participants

(MGH, BWH)

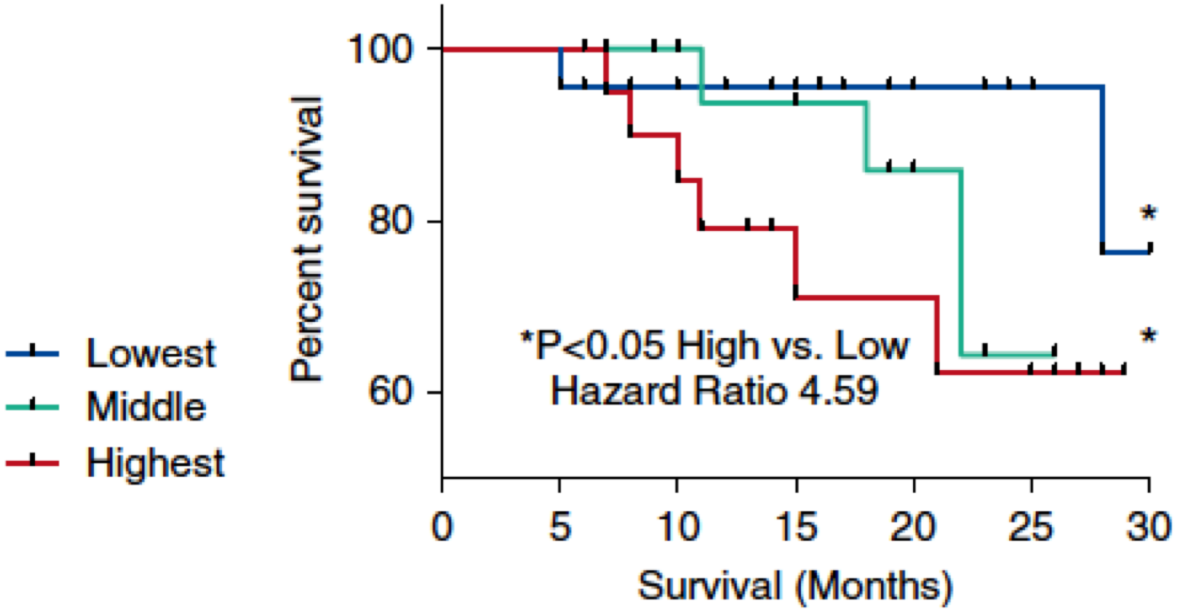
Nitto

Innovation for Customers

Do the bacteria in the lung play a role in IPF?



64 IPF
17 COPD
27 Healthy controls



Molyneaux et al. Am J Respir Crit Care Med Vol 190, Iss 8, pp 906–913, Oct 15, 2014

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

Clinical trials number NCT02759120

Comparing standard care with either trimethoprim/sulfamethoxazole or doxycycline for 36 months

Genetics and personalized medicine

- Polymorphisms on chromosome 11p15 are known risk factors for IPF:
  - Mucin 5B (MUC5B)
  - Toll-interacting protein (TOLLIP) locus
- Can genetic factors predict an individual response to IPF therapy?
- Should we revisit agents previously deemed ineffective in larger studies?

ORIGINAL ARTICLE

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

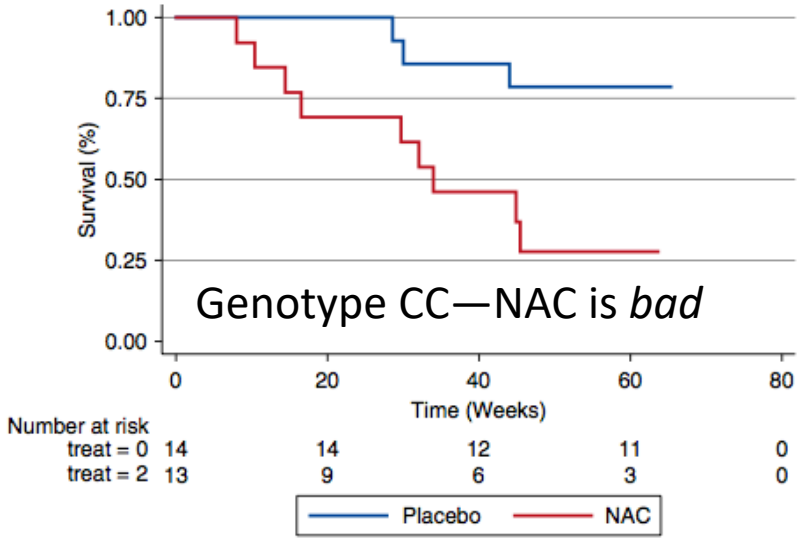
Justin M. Oldham[1*], Shwu-Fan Ma[1*], Fernando J. Martinez[2], Kevin J. Anstrom[3], Ganesh Raghu[4], David A. Schwartz[5], Eleanor Valenzi[1], Leah Witt[1], Cathryn Lee[1], Rekha Vij[1], Yong Huang[1], Mary E. Strek[1], and Imre Noth[1]; for the IPFnet Investigators

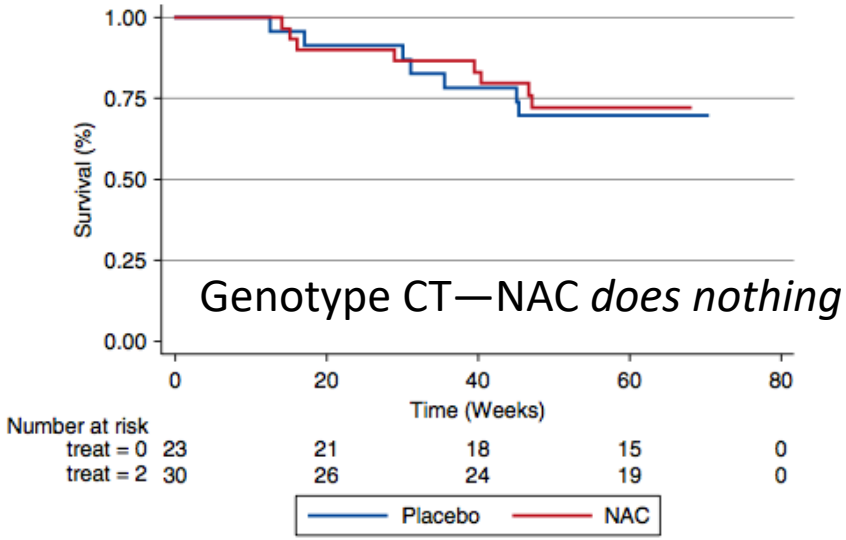
Post-hoc analysis of subjects enrolled in the PANTHER-IPF study (Prednisone, Azathioprine, NAC)

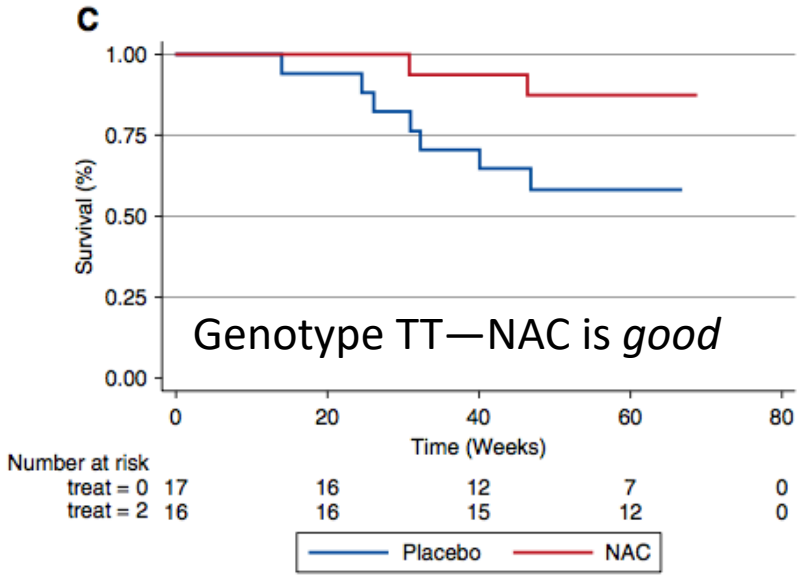
154 patients were analyzed

- 54 placebo
- 60 NAC
- 40 NAC, Azathioprine, prednisone

TOLLIP genotype is associated with outcomes in IPF patients treated with NAC







Oldham et al. Am J Respir Crit Care Med. 2015 Dec 15;192(12):1475-82

96 Studies found for: **Idiopathic pulmonary fibrosis | Recruiting Studies**

Also searched for **Lungs**. See Search Details

Applied Filters: ☑ **Recruiting**

Active drug trials in IPF

Company	Drug name	Mechanism of action	Phase of trial
Toray Industries	TRK-250	Inhibits TGF-β1 expression	Phase 1
Novartis	VAY736 (Ianalumab)	Anti-B-cell activating factor receptor antibody	Phase 2
Pliant Therapeutics	PLN-74809	Inhibitor of αvβ1 / αvβ6	Phase 2
Algernon Pharmaceuticals	NP-120 (Ifenprodil)	NDMA glutamate Receptor antagonist	Phase 2
Celgene	CC-90001	Jun N-Terminal Kinase (JNK) Inhibitor	Phase 2
Nitto	ND-L02-s0201	siRNA that inhibits HSP47	Phase 2
Galecto Biotech	TD139	Galectin-3 inhibitor	Phase 2
Galapagos	GLPG1690	Autotaxin inhibitor	Phase 3
FibroGen	Pamrevlumab	Antibody against (CTGF)	Phase 3

Summary

Although we still don’t have a cure for IPF, we have gained a MUCH better understanding of its pathophysiology

Nintedanib and pirfenidone, while a step in the right direction, will only be the tip of the iceberg when it comes to treating this disease

There are numerous promising drug trials on the horizon

Thank you for your courage and inspiration.

Stay safe!