

# Shifting Paradigms of IPF Pathogenesis

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# History of “Idiopathic Pulmonary Fibrosis”

1892 – Osler: “cirrhosis of the lung”



Arnold Rich and Louis Hamman  
[www.hopkinsmedicine.org](http://www.hopkinsmedicine.org)

1935 – Hamman and Rich: “Fulminating Diffuse Interstitial Fibrosis of the Lungs”

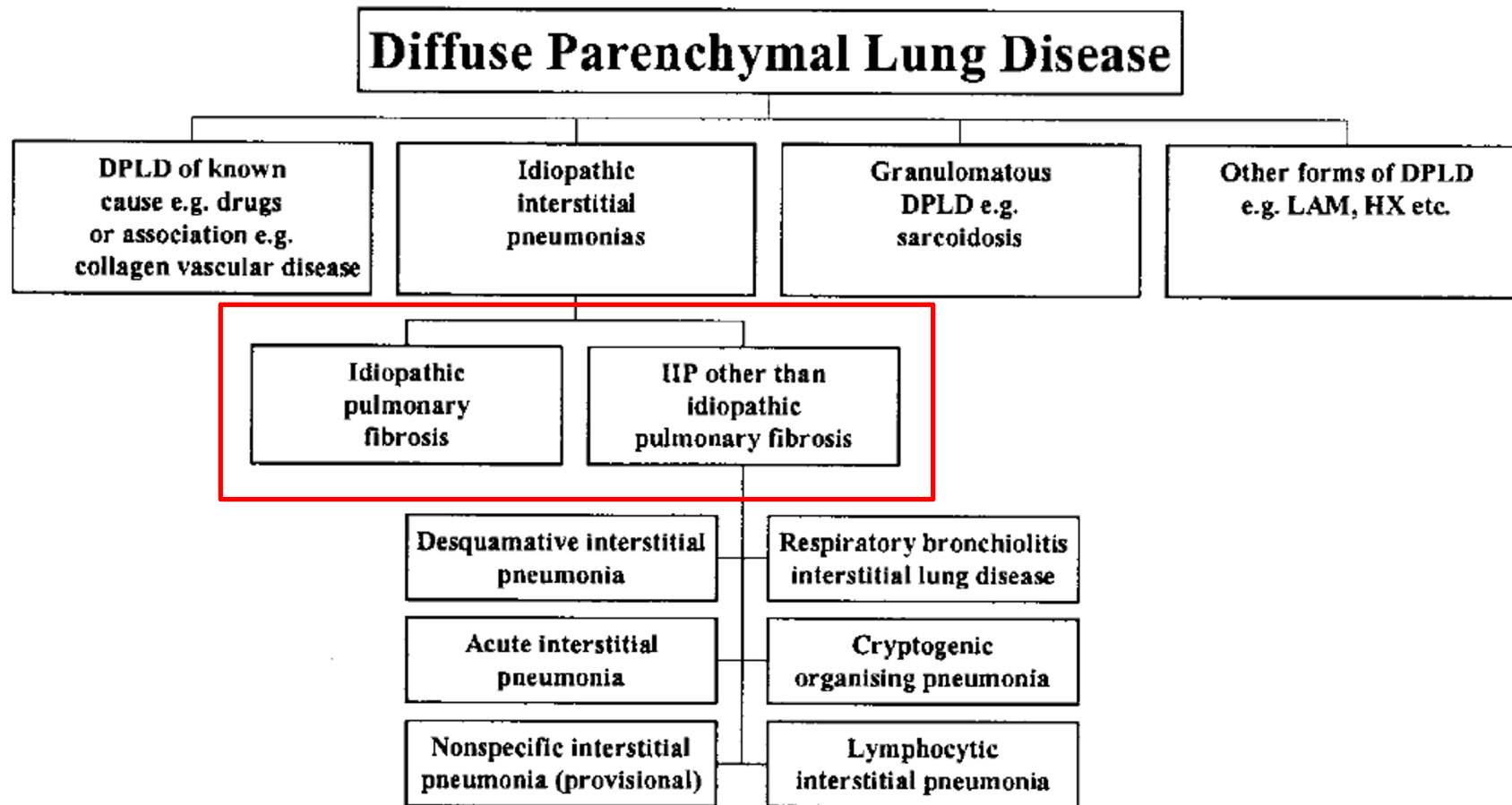
- *“...this [pathological] lesion was so extraordinary and distinctive that there can be little doubt that the symptoms displayed by each case, widely different though they were, arose from the same underlying morbid process.”*

# IPF History – Disease Classification

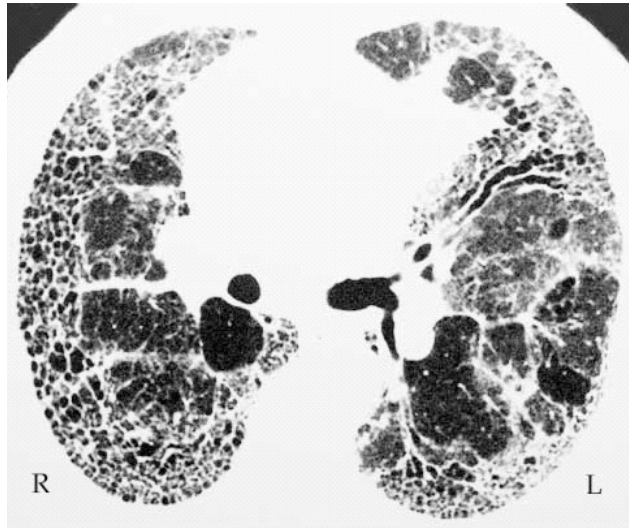
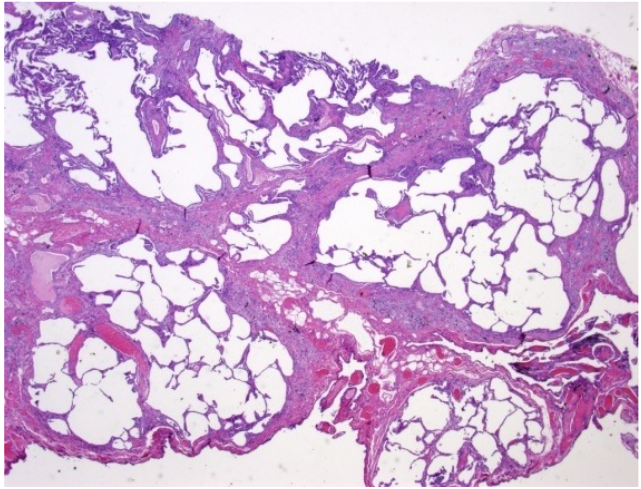
- 1969 – Liebow and Carrington: described 5 histological “subtypes” of IPF:
    - Most common: “Usual” interstitial pneumonia (UIP)
    - Desquamative interstitial pneumonia (DIP)
    - Others: lymphoid interstitial pneumonia (LIP), bronchiolitis interstitial pneumonia (BIP), giant cell interstitial pneumonia (GIP)
  - 1998 – Katzenstein and Myers: reclassification of IPF histological subtypes
    - UIP
    - DIP
    - Acute interstitial pneumonia (AIP)
    - Nonspecific interstitial pneumonia (NSIP)
- } Separate clinical entities - differed in clinical features, natural history, and response to Rx



# Classification of ILDs (a.k.a. DPLDs)



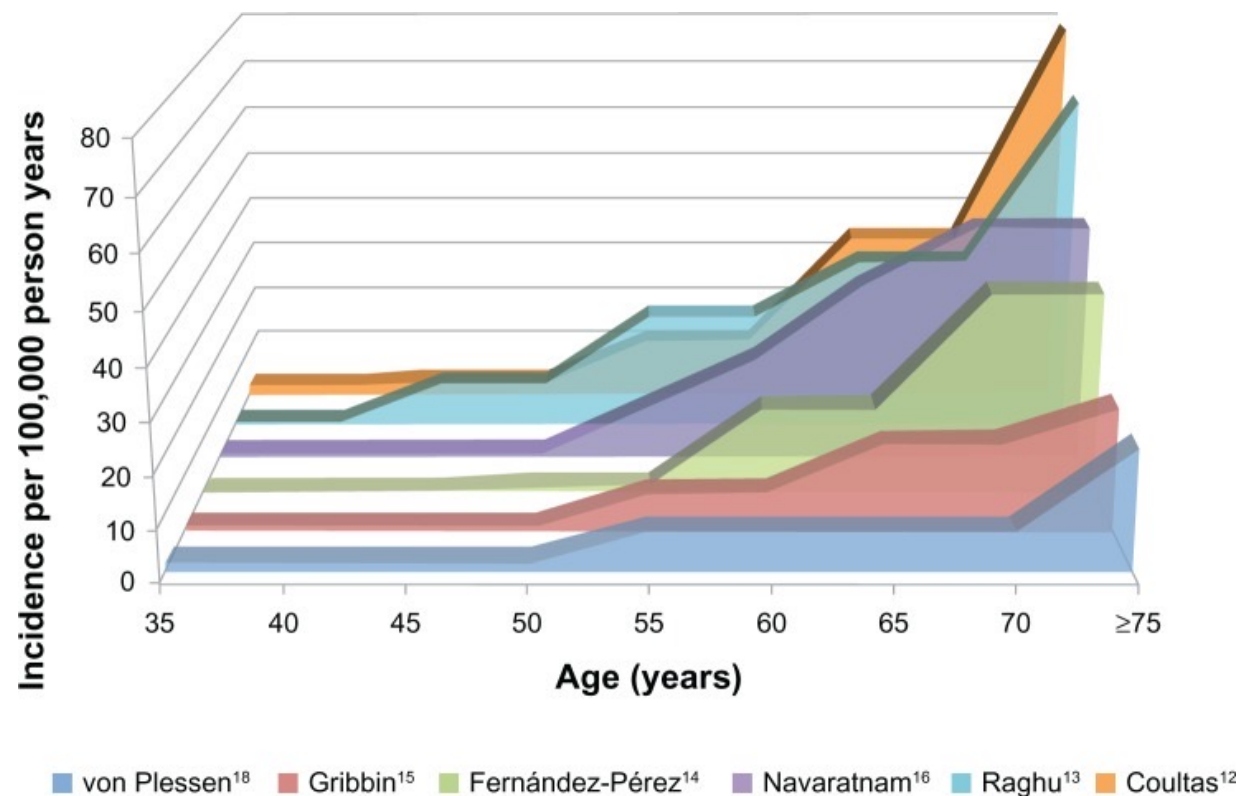
# Idiopathic Pulmonary Fibrosis (IPF)



- Most common idiopathic ILD
- Progressive replacement of normal lung tissue with fibrosis (scarring)
- Histology: usual interstitial pneumonia (UIP)
- Characteristic HRCT findings
- Diagnosis of exclusion!
  - Connective tissue disease
  - Asbestosis
  - Hypersensitivity pneumonitis

# Idiopathic Pulmonary Fibrosis (IPF)

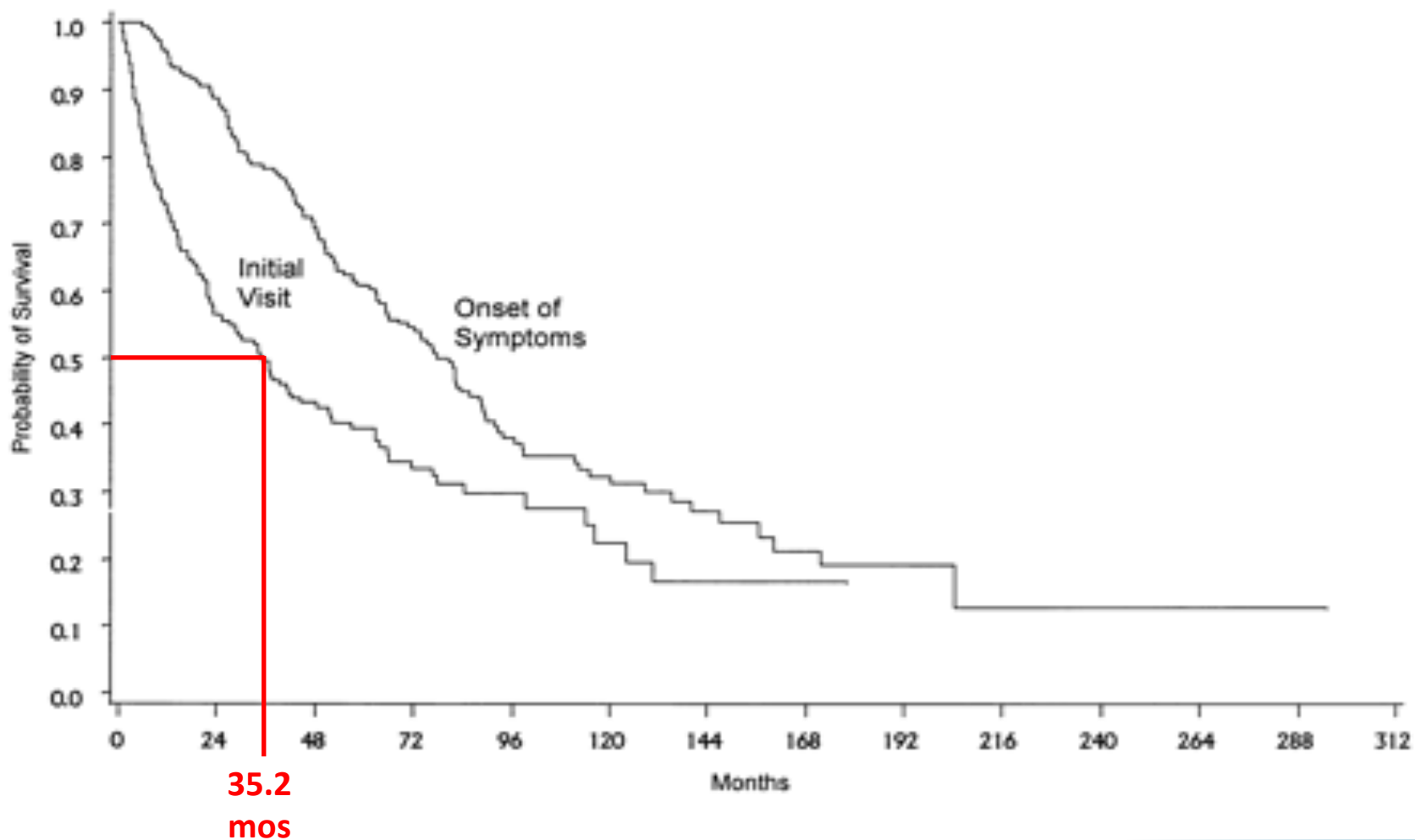
- Risk factors:
  - Age
  - Male sex (~2:1)
  - Cigarette smoking
  - Family history (~20%)
  - Genetic predispositions
    - Telomerase genes (*TERT*, *TERC*, *RTEL1*, *PARN*, *DKC1*)
    - Surfactant protein genes (*SFTPC* and *SFTPA2*)
    - Mucin genes (*MUC5B*)



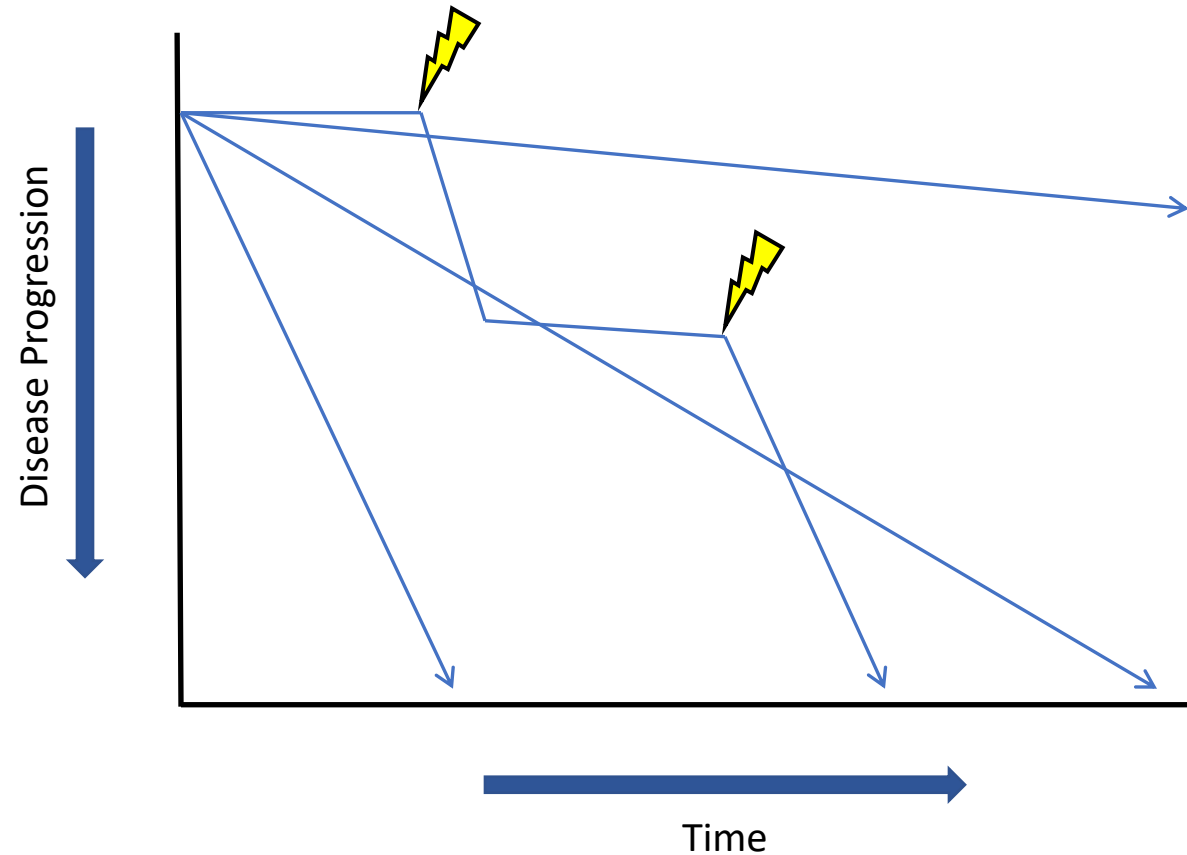
Ley and Collard. *Clin Epidemiol.* 2013;5:483-92.



# IPF has a poor prognosis



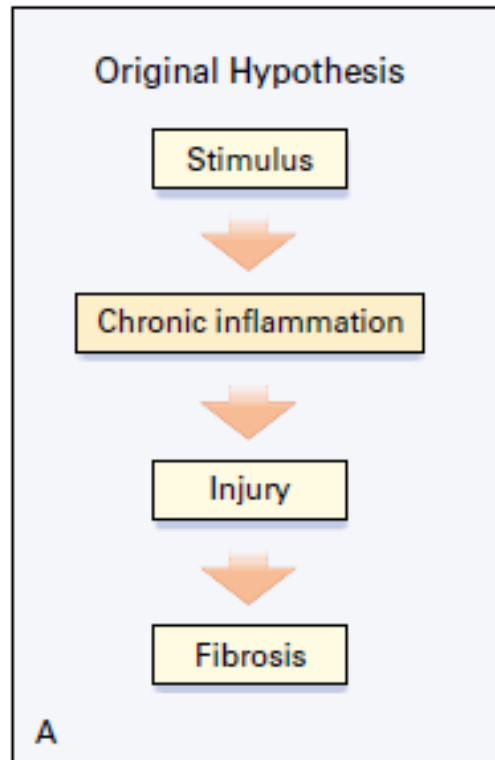
# Heterogeneity of Disease Progression in IPF



Adapted from Ley et al. *AJRCCM*. 2011;183:431-40.



# IPF Pathogenesis – Inflammation Hypothesis



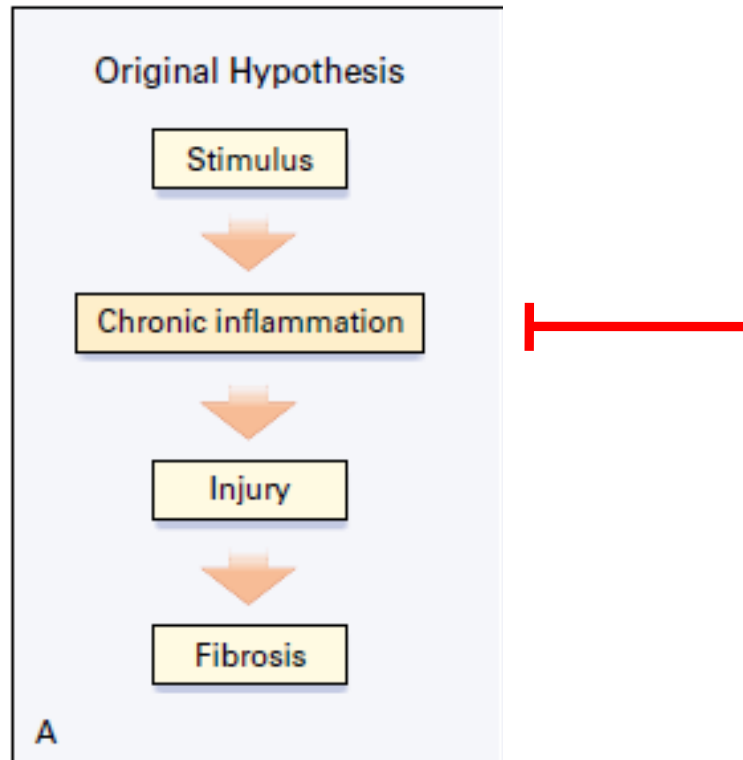
R. G. Crystal (1976)

- BAL and  $^{67}\text{Ga}$ -scanning on IPF patients and controls

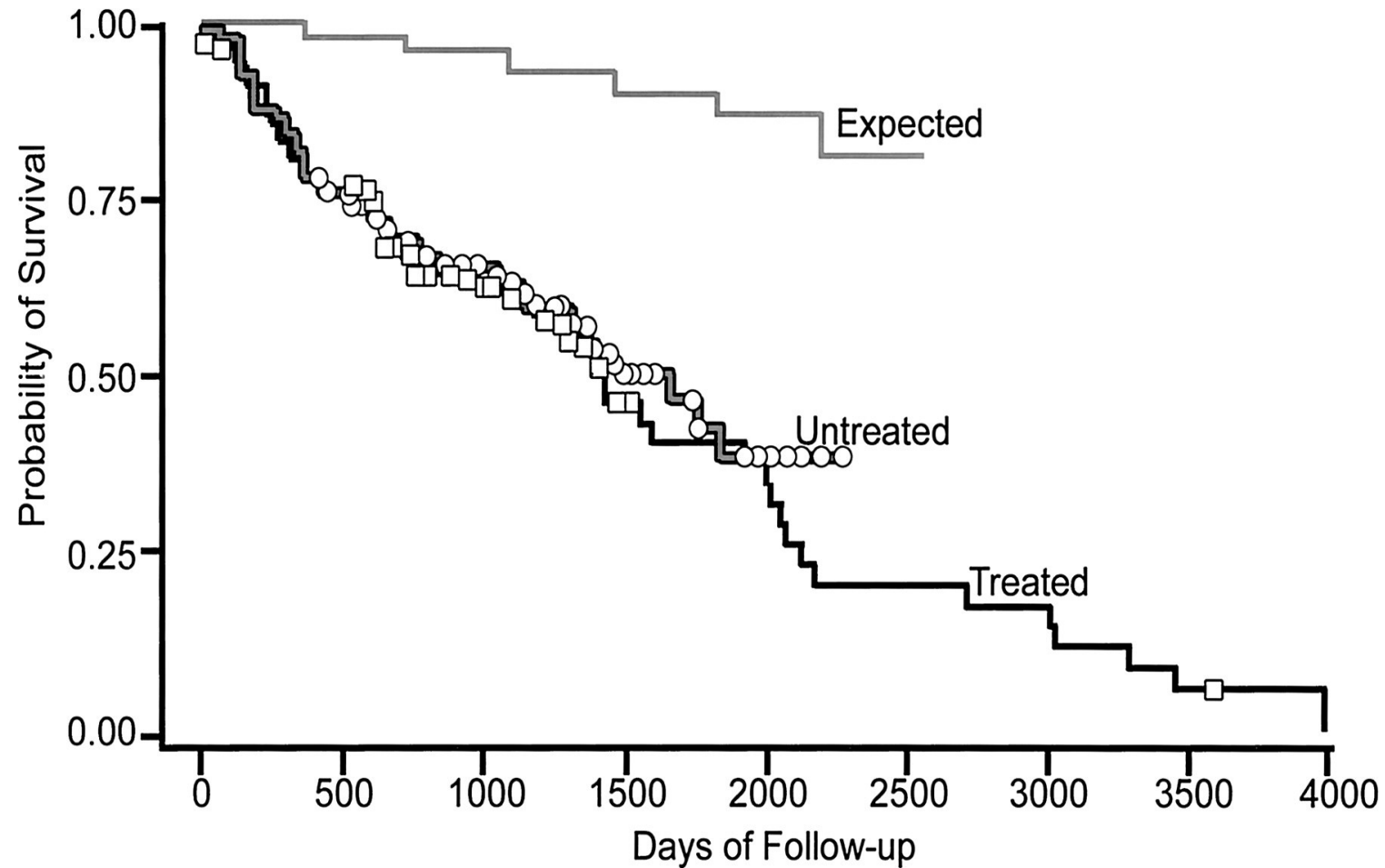
	Controls§	Idiopathic Pulmonary Fibrosis‡	
		Without Therapy	With Therapy
Cells**			
Neutrophils	0-3	I (3+) ††	I (2+)
Lymphocytes	8-18	N	N
Eosinophils	0	I (1+)	I (1+)
Alveolar macrophages	80-89	D (3+)	D (1+)

*“The fibrotic process is probably irreversible, but the inflammatory and immune processes that cause it may be amenable to therapy if diagnosed early.”*

# IPF Pathogenesis – Inflammation Hypothesis



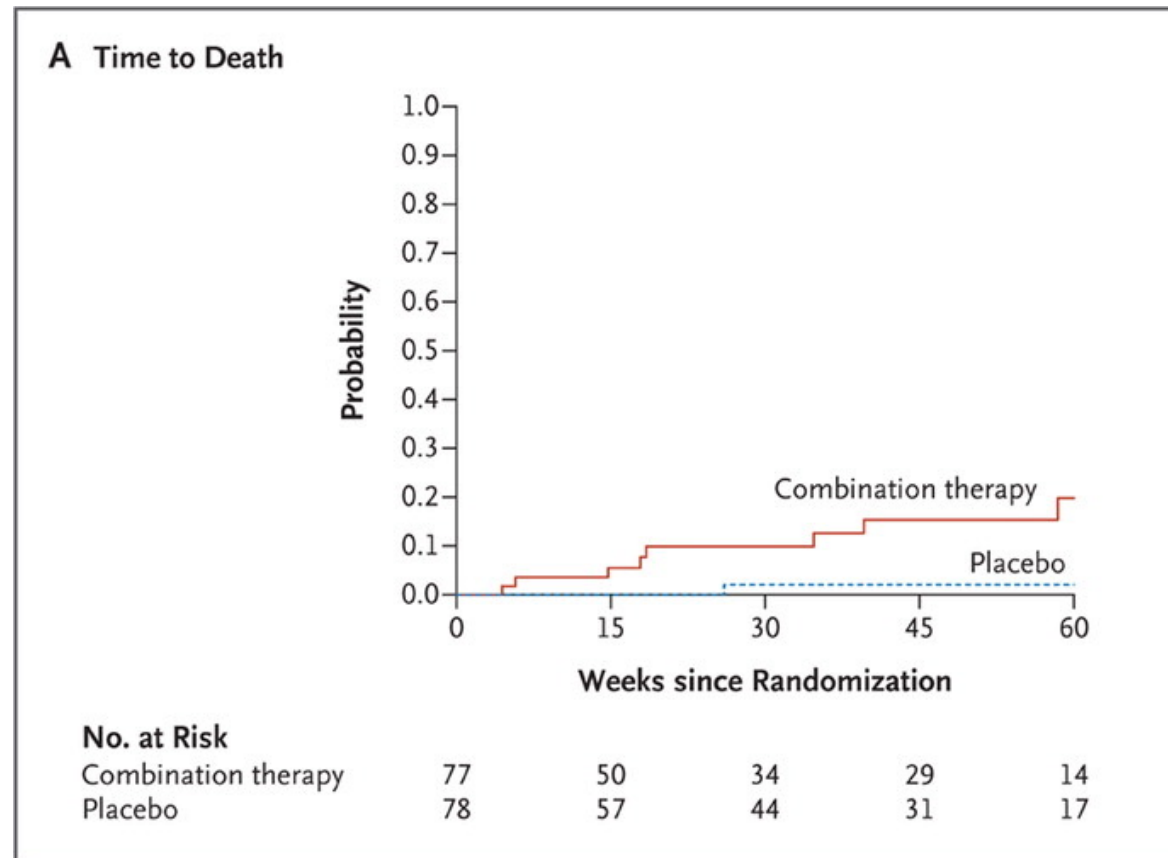
# Anti-inflammatory Therapy is Ineffective in IPF



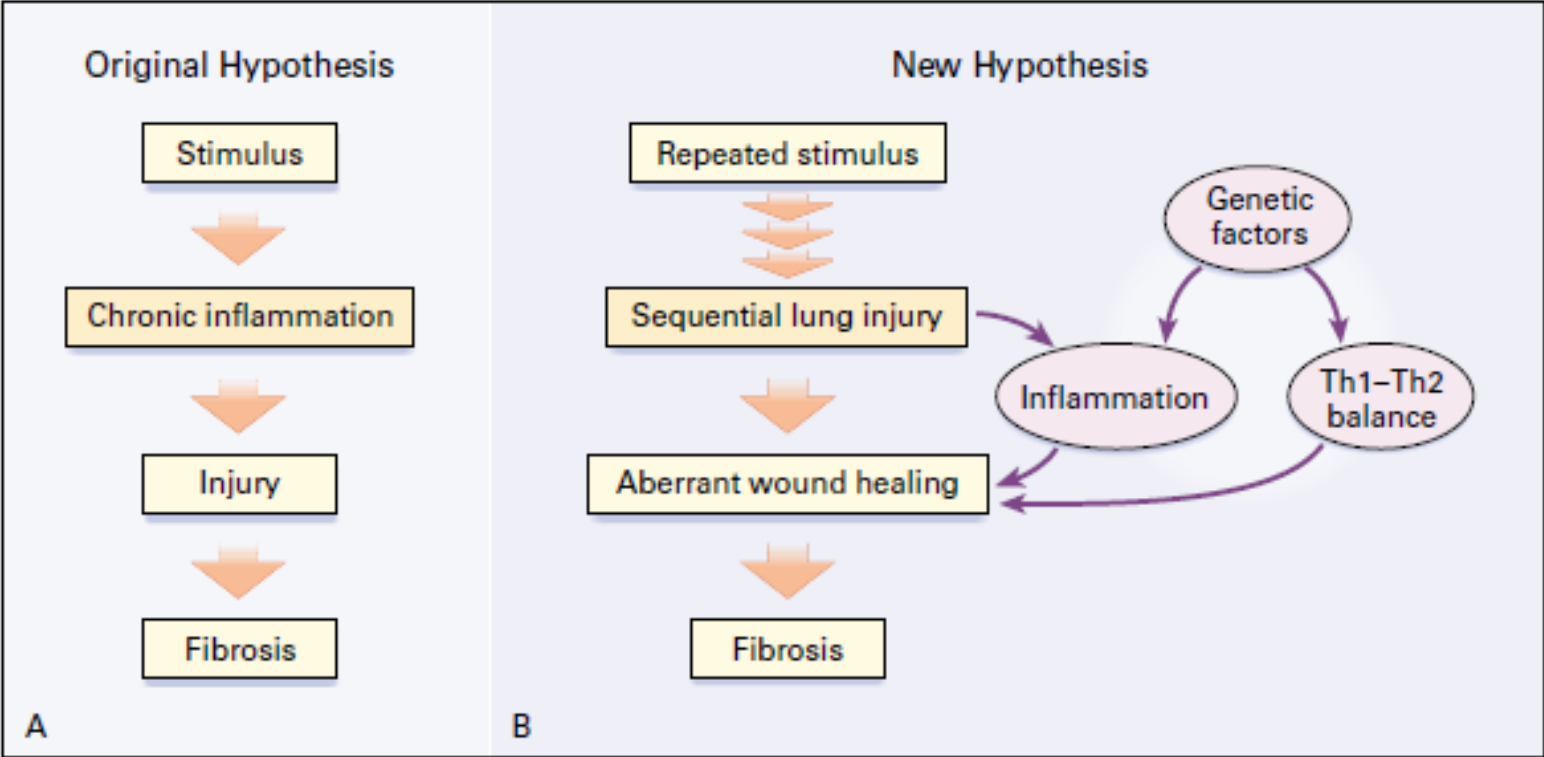
# Anti-inflammatory therapy may be harmful in IPF

## PANTHER Study – Pred/Aza/NAC vs. NAC vs. Placebo

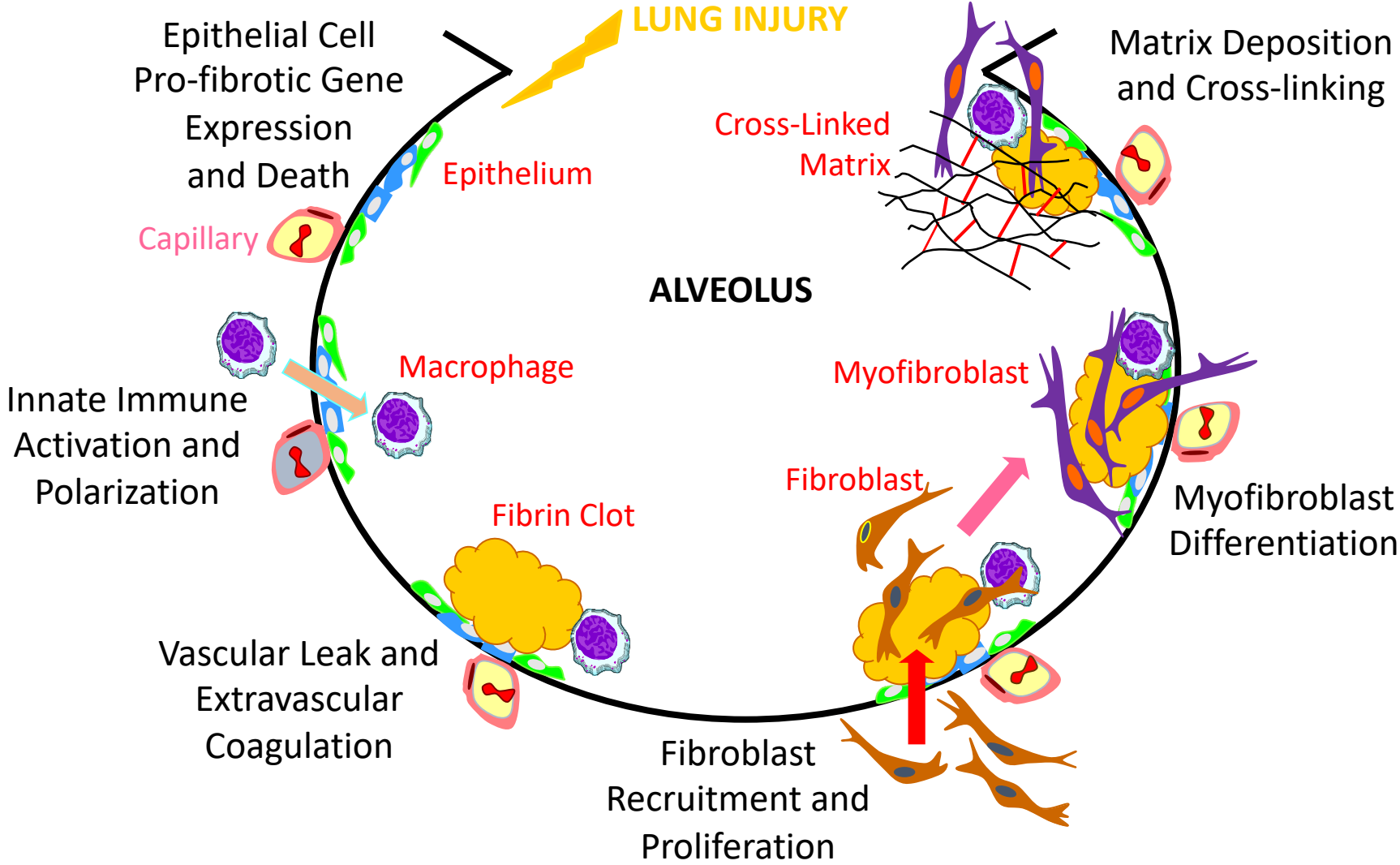
- Triple therapy arm stopped at mid-point analysis (mean follow-up 32 weeks)



# IPF Pathogenesis – A Shifting Paradigm

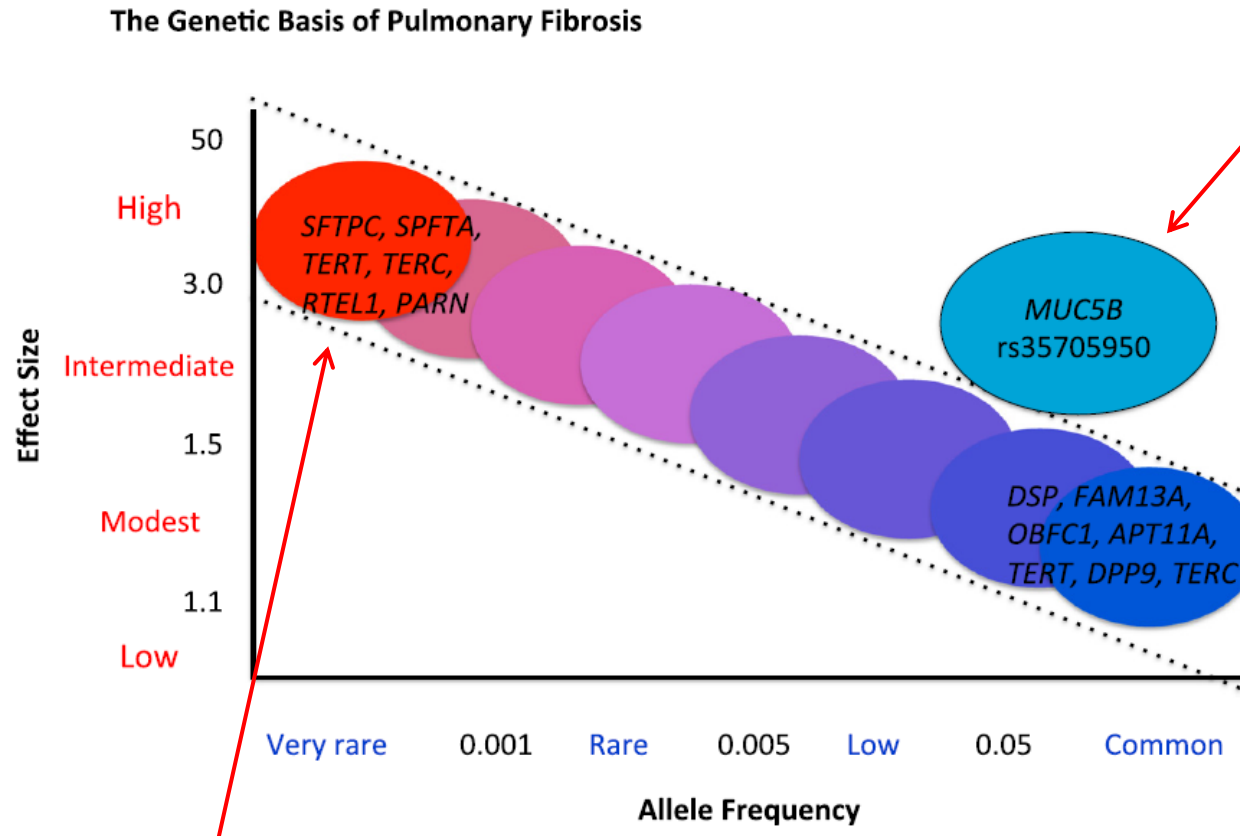


# Aberrant Wound-Healing Paradigm of IPF



Modified from: Selman M et al. *Ann Intern Med.* 2001

# IS IPF A GENETIC DISEASE?



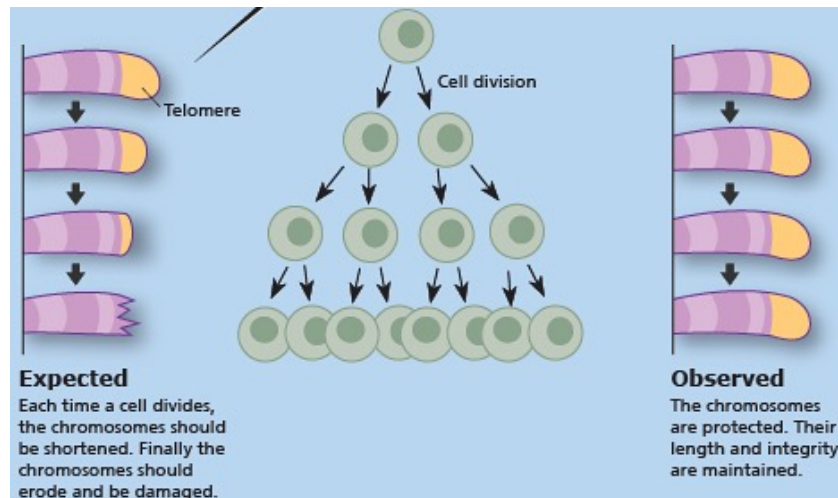
## MUC5B POLYMORPHISM

- MAF ~10%
- >5X AND >18X RISK OF IPF WITH 1 OR 2 COPIES

## RARE VARIANTS/MEDELIAN INHERITANCE

- IDENTIFIED IN ~1/3 OF FAMILIAL PF

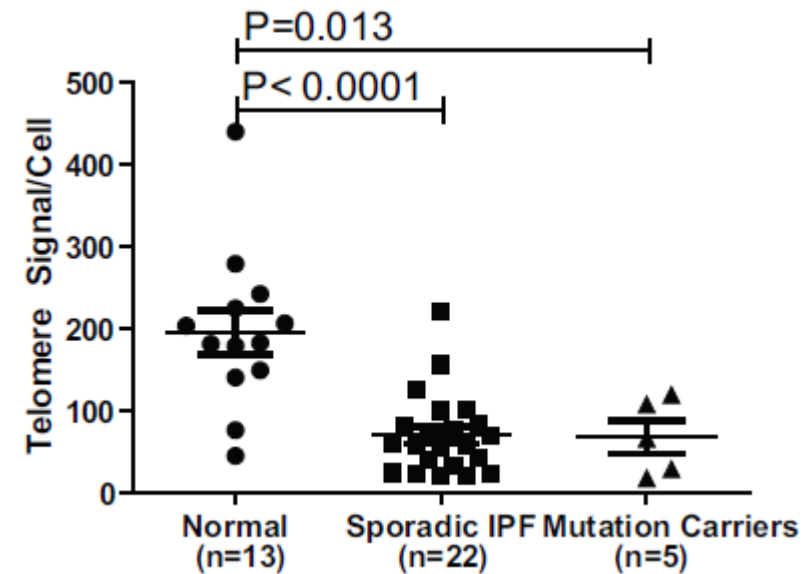
# Shortened Telomeres in IPF – a Link to Aging?



[www.nobelprize.org](http://www.nobelprize.org); 2009

- Pulmonary fibrosis a common feature of dyskeratosis congenita
- *TERT* and *TERC* mutations identified in familial IPF (Tsakiri et al. *PNAS*. 2007;104:7552-7)
- Shortened telomeres in IPF alveolar epithelial cells

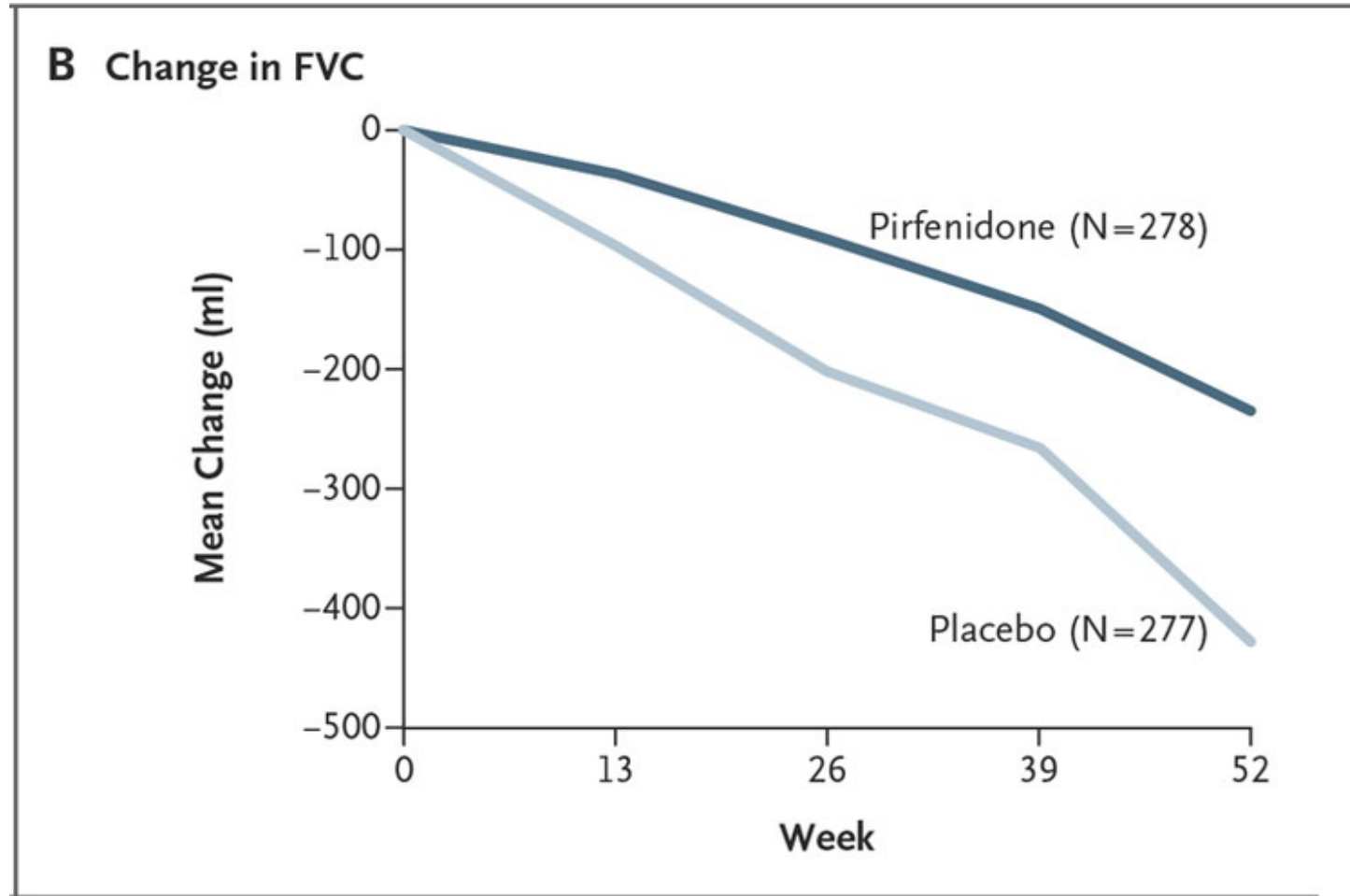
- Telomerase complex maintains telomeres after cell division
- Loss of telomere length associated with aging/cellular senescence



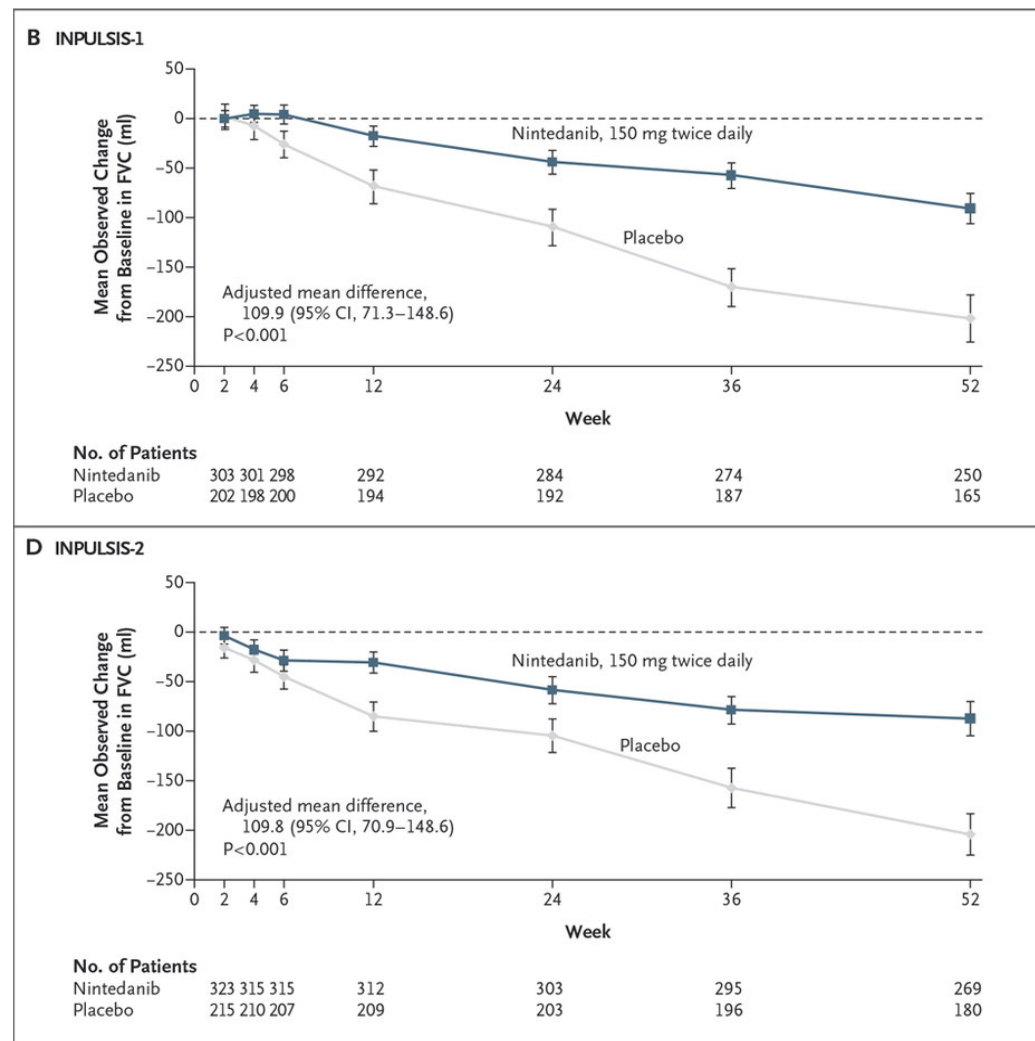
Adler et al. *PNAS*. 2008;105:13051-6



# New Therapies for IPF - Pirfenidone



# New Therapies for IPF – Nintedanib





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### FDA News Release

# FDA approves Esbriet to treat idiopathic pulmonary fibrosis

**For Immediate Release**

October 15, 2014

## FDA approves Ofev to treat idiopathic pulmonary fibrosis

**For Immediate Release**

October 15, 2014

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# Potential PF therapies on the horizon?

