ILD Collaborative

Project ECHO

Shifting Paradigms of IPF Pathogenesis

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MGH Interstitial Lung Disease Program

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History of "Idiopathic Pulmonary Fibrosis"

1892 – Osler: "cirrhosis of the lung"

Arnold Rich and Louis Hamman
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."*

Osler W. The Principles and Practice of Medicine. New York. 1892.
Hamman and Rich. *Trans Am Clin Climatol Assoc*. 1935. 51:154-163.

IPF History – Disease Classification

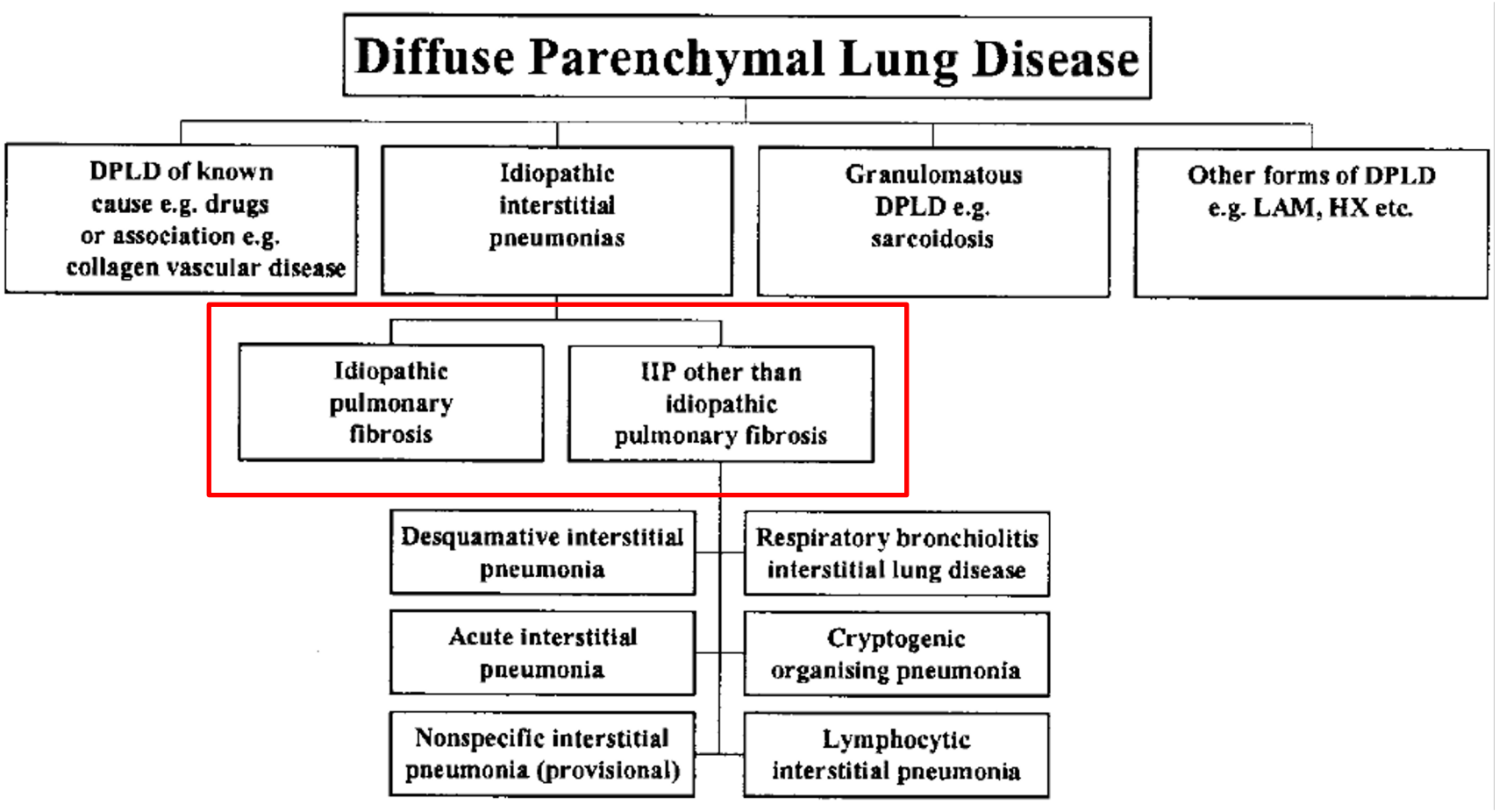
- 1969 – Liebow and Carrington: described 5 histological "subtypes" of IPF:
  - Most common: "Usual" interstitial pneumonia (UIP)
  - Desquamative interstitial pneumonia (DIP)
  - Others: lymphoid interstitial pneumonia (LIP), bronchiolitis interstitial pneumonia (BIP), giant cell interstitial pneumonia (GIP)

- 1998 – Katzenstein and Myers: reclassification of 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

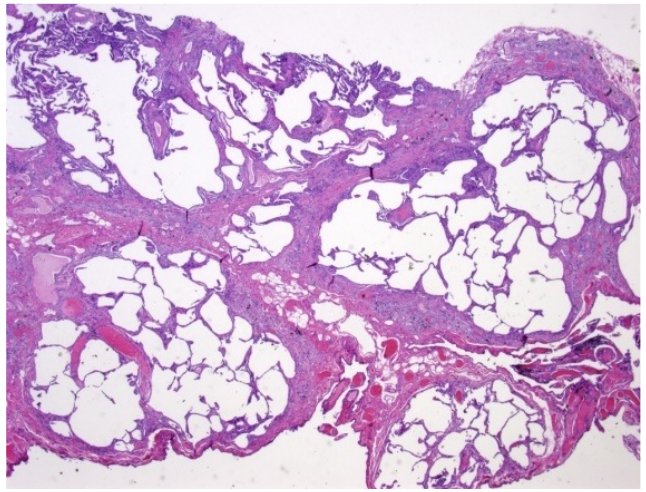
Liebow and Carrington. Frontiers of Pulmonary Radiology. 1969:102-141.
Katzenstein ALA and Myers JL. *Am J Resp Crit Car Med.* 1998;85:769-88.

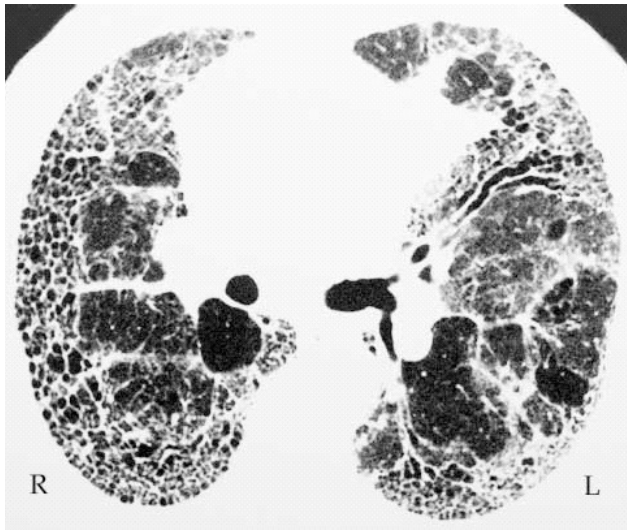
Classification of ILDs (a.k.a. DPLDs)



ATS/ERS Consensus Statement on IPF. 2000 and 2011.
ATS/ERS Consensus Statement on IIPs. *Am J Resp Crit Car Med.* 2002.

Idiopathic Pulmonary Fibrosis (IPF)

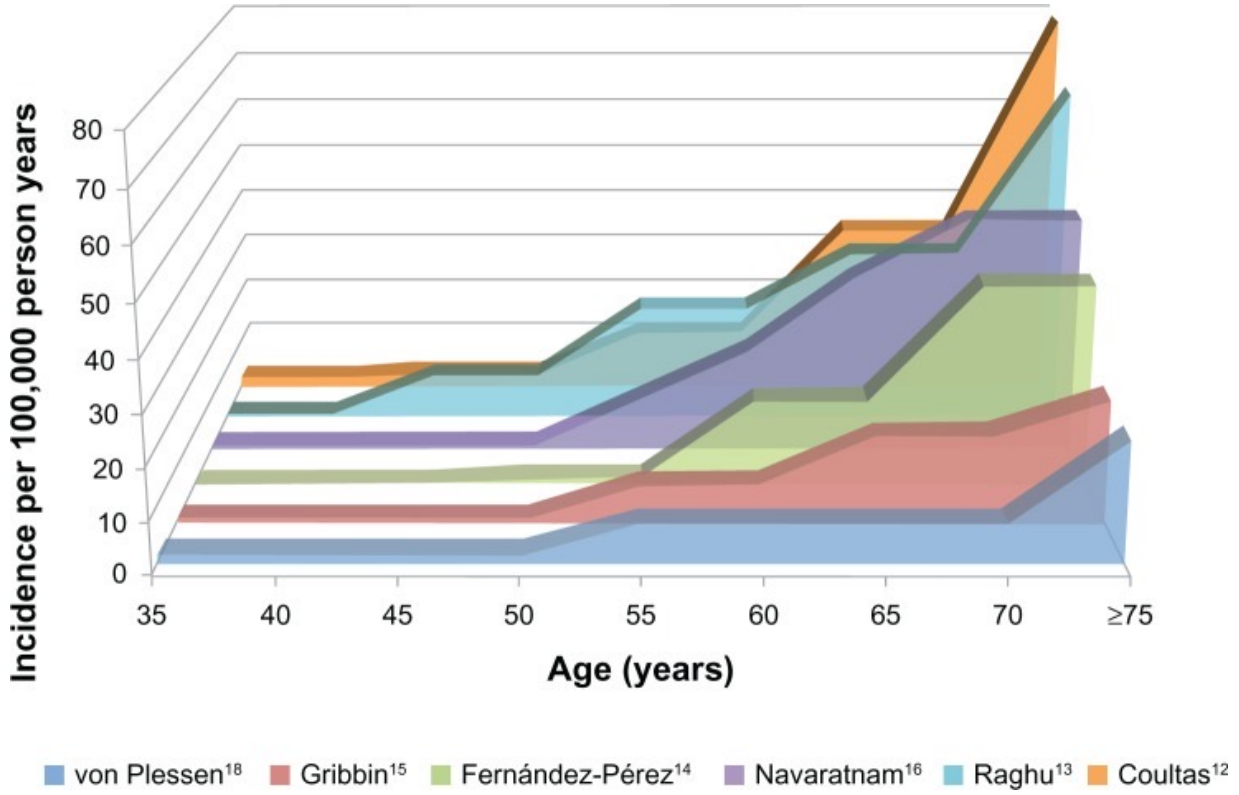




- Most common idiopathic ILD
- Progressive replacement of normal lung tissue with fibrosis (scarring)
- Histology: usual interstitial pneumonia (UIP)
- Characteristic HRCT findings
- Diagnosis of exclusion!
  - Connective tissue disease
  - Asbestosis
  - Hypersensitivity pneumonitis

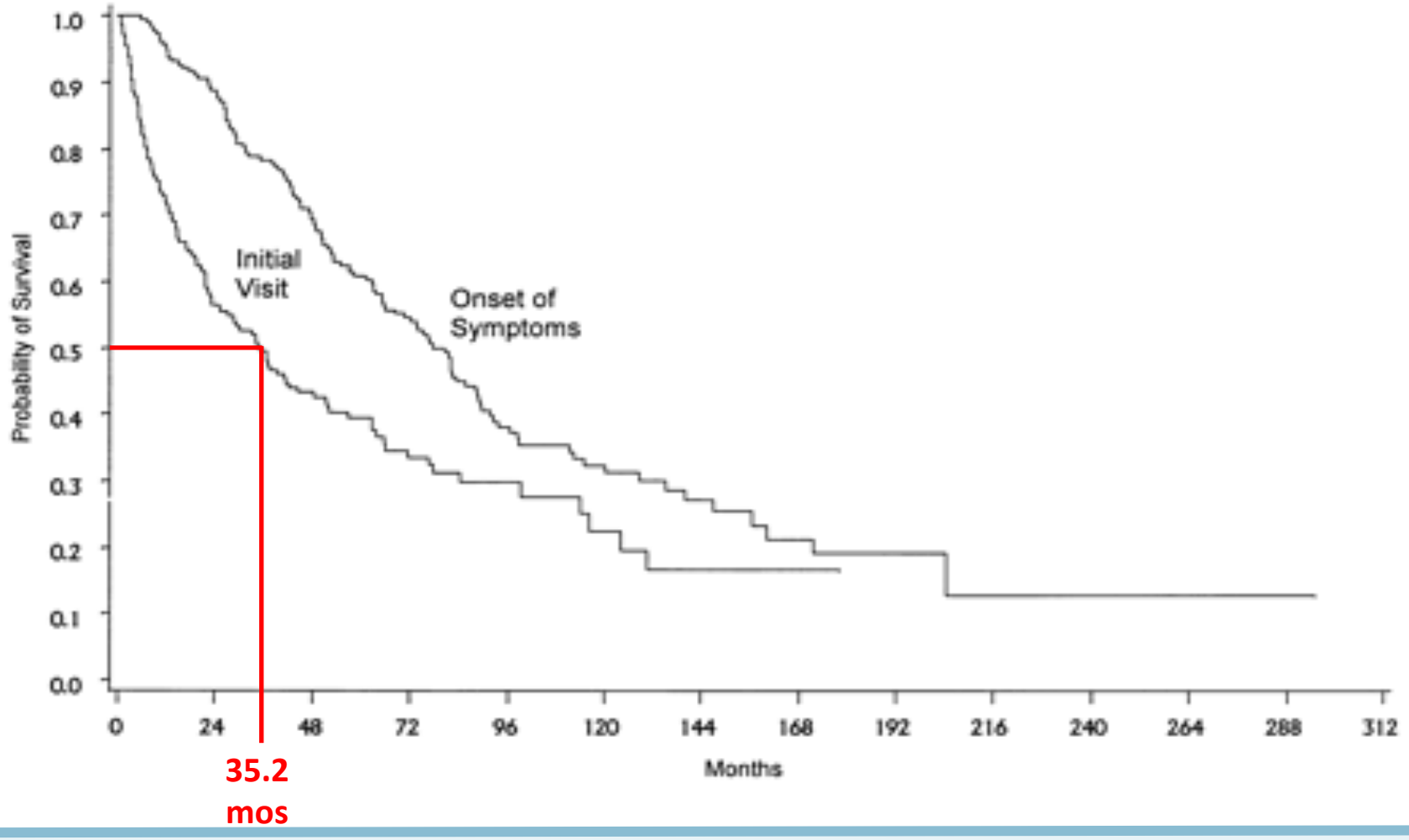
Idiopathic Pulmonary Fibrosis (IPF)

- 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)



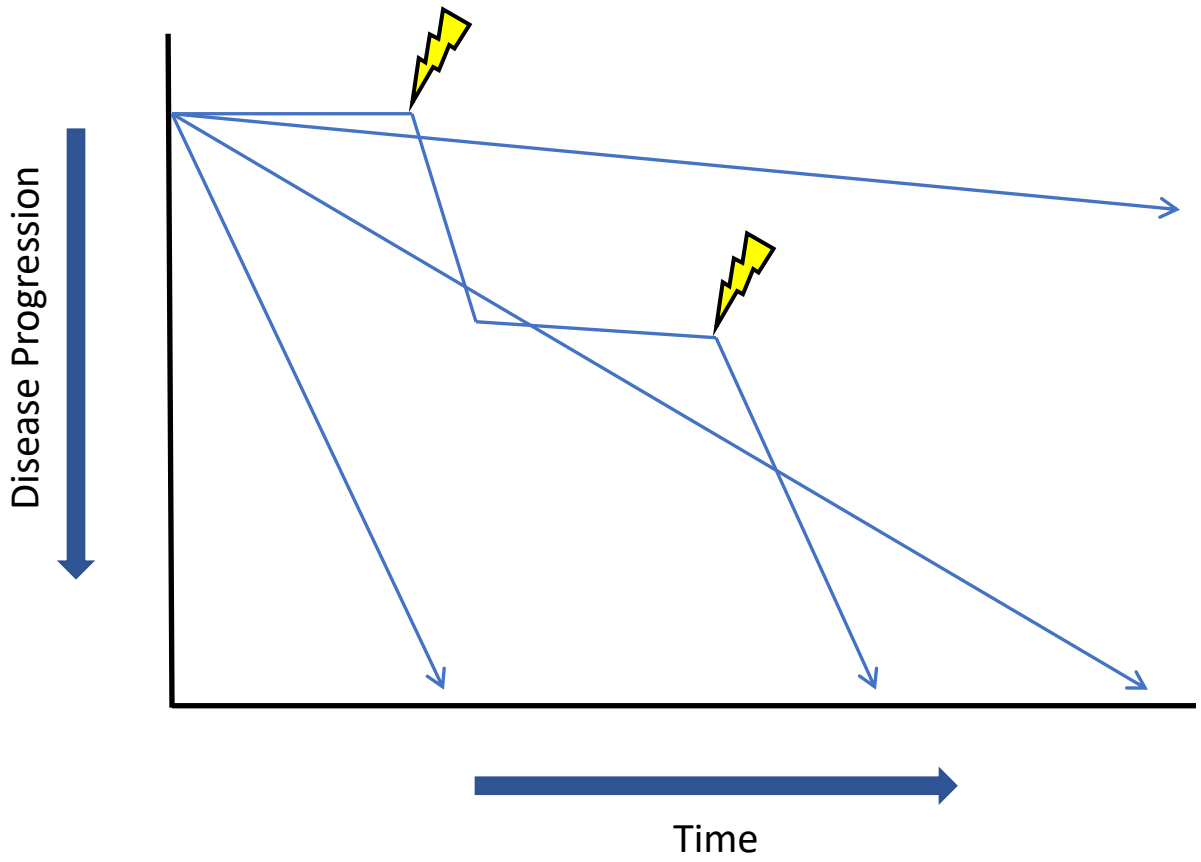
Ley and Collard. *Clin Epidem.* 2013;5:483-92.

IPF has a poor prognosis



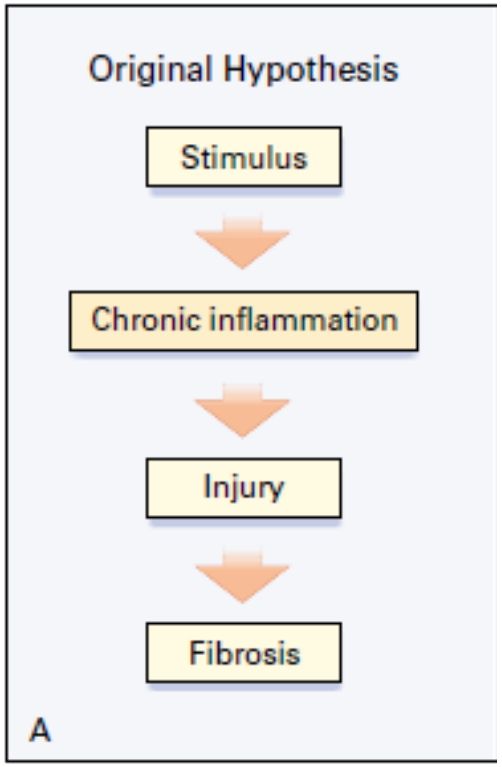
King TE et al. *AJRCCM.* 2001

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}Ga-scanning on IPF patients and controls

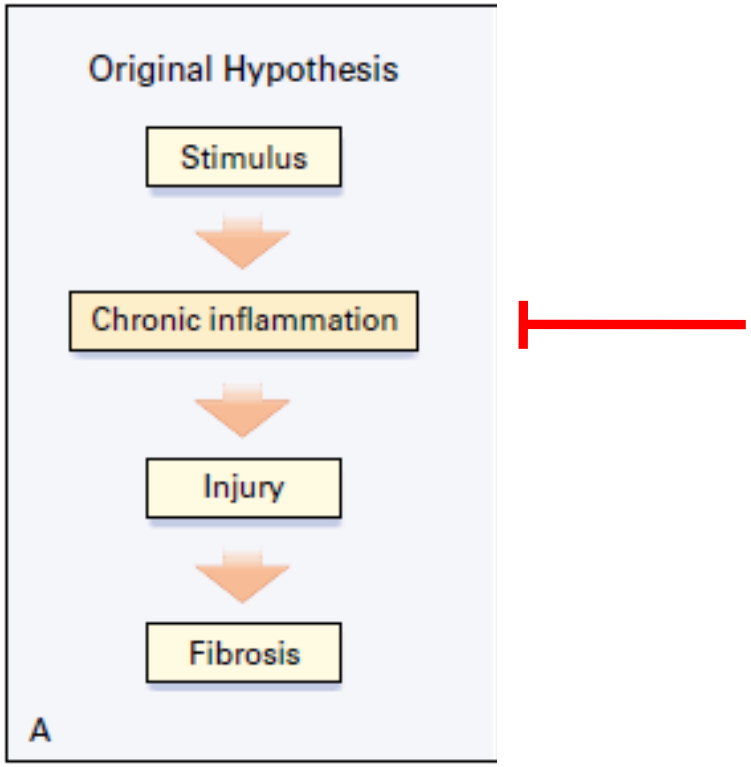
	Controls§	Idiopathic Pulmonary Fibrosis‡	
		Without Therapy	With Therapy
Cells**			
Neutrophils	0-3	I (3+)††	I (2+)
Lymphocytes	8-18	N	N
Eosinophils	0	I (1+)	I (1+)
Alveolar macrophages	80-89	D (3+)	D (1+)

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

Gross and Hunninghake. *NEJM.* 2001;345(7):517-25

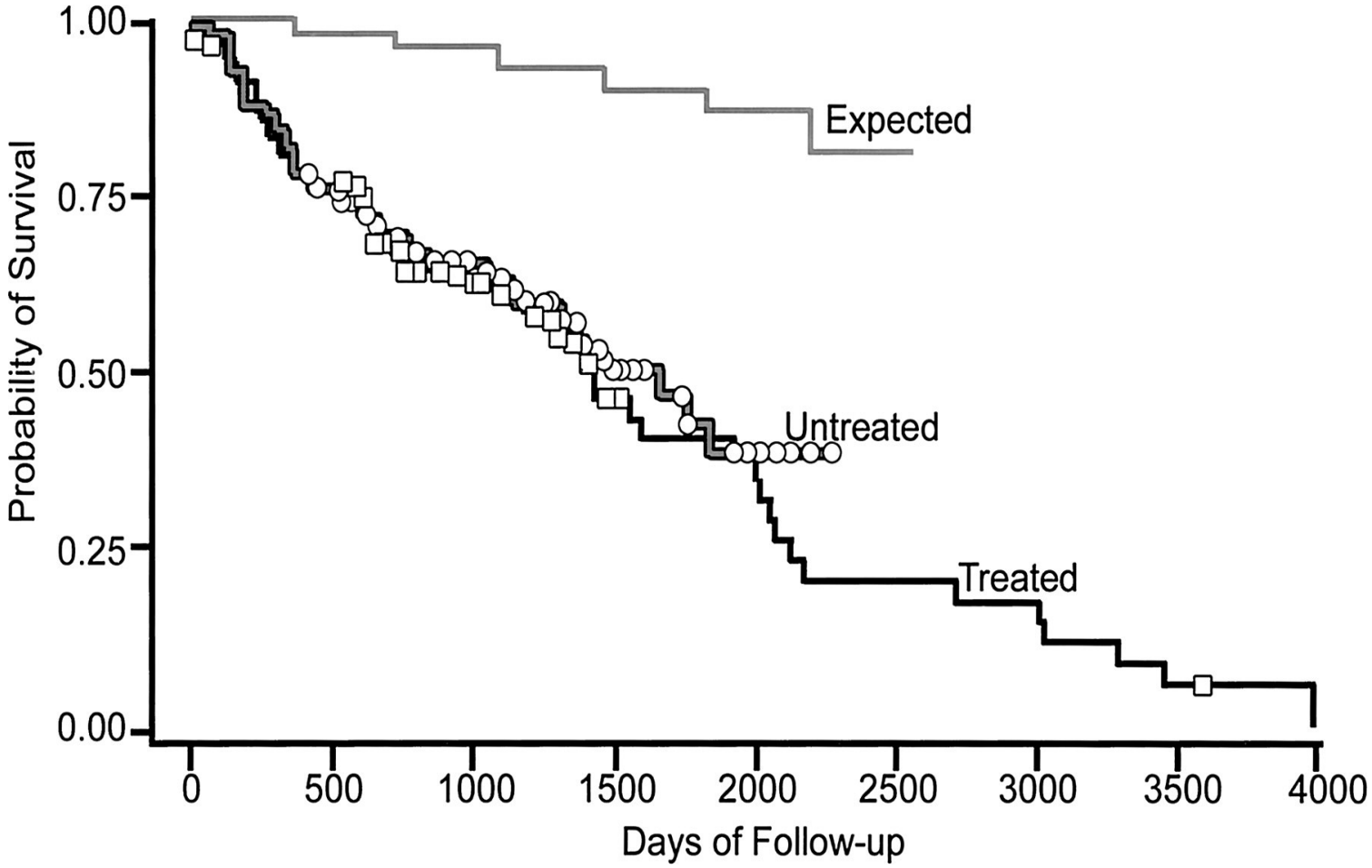
Crystal RG et al. Ann Int Med. 1976;85:769-88.

IPF Pathogenesis – Inflammation Hypothesis



Gross and Hunninghake. *NEJM.* 2001;345(7):517-25

Anti-inflammatory Therapy is Ineffective in IPF

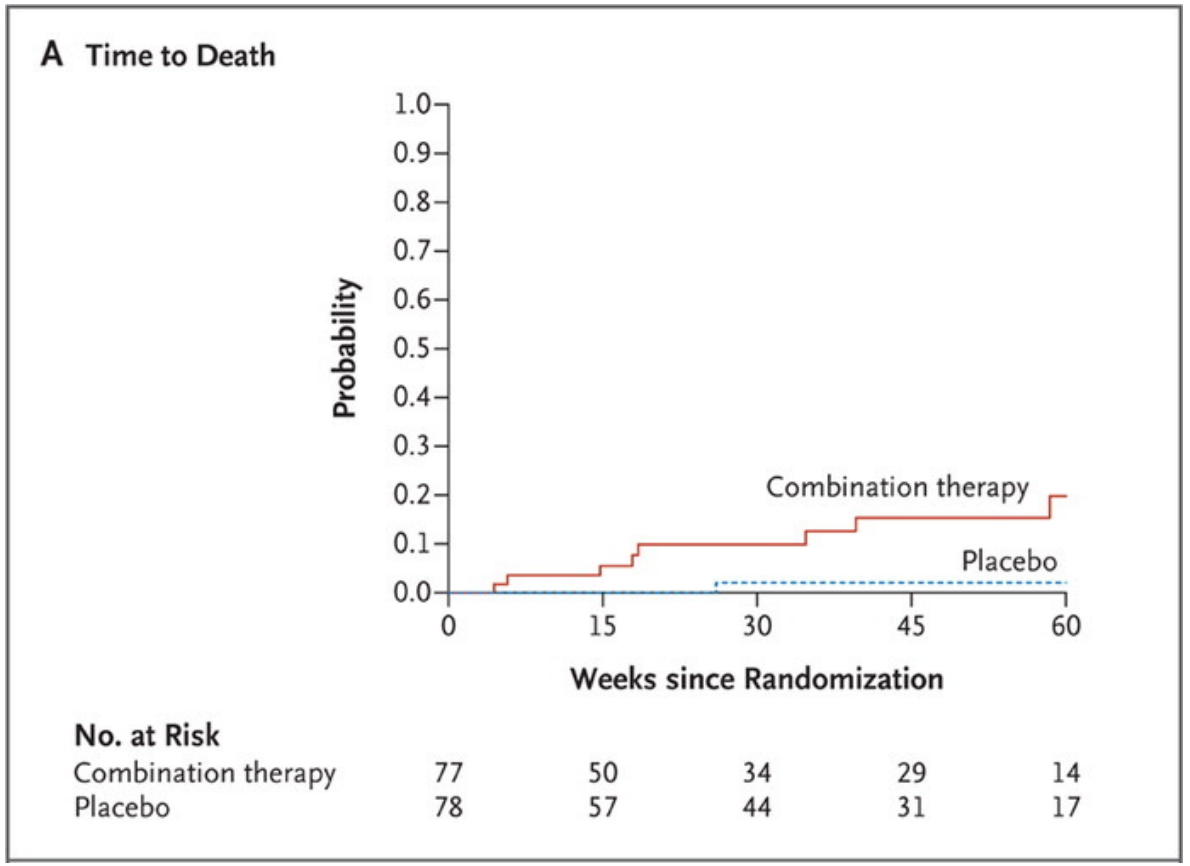


Collard HR, et al. *Chest* 2004;125:2169-2174

Anti-inflammatory therapy may be harmful in IPF

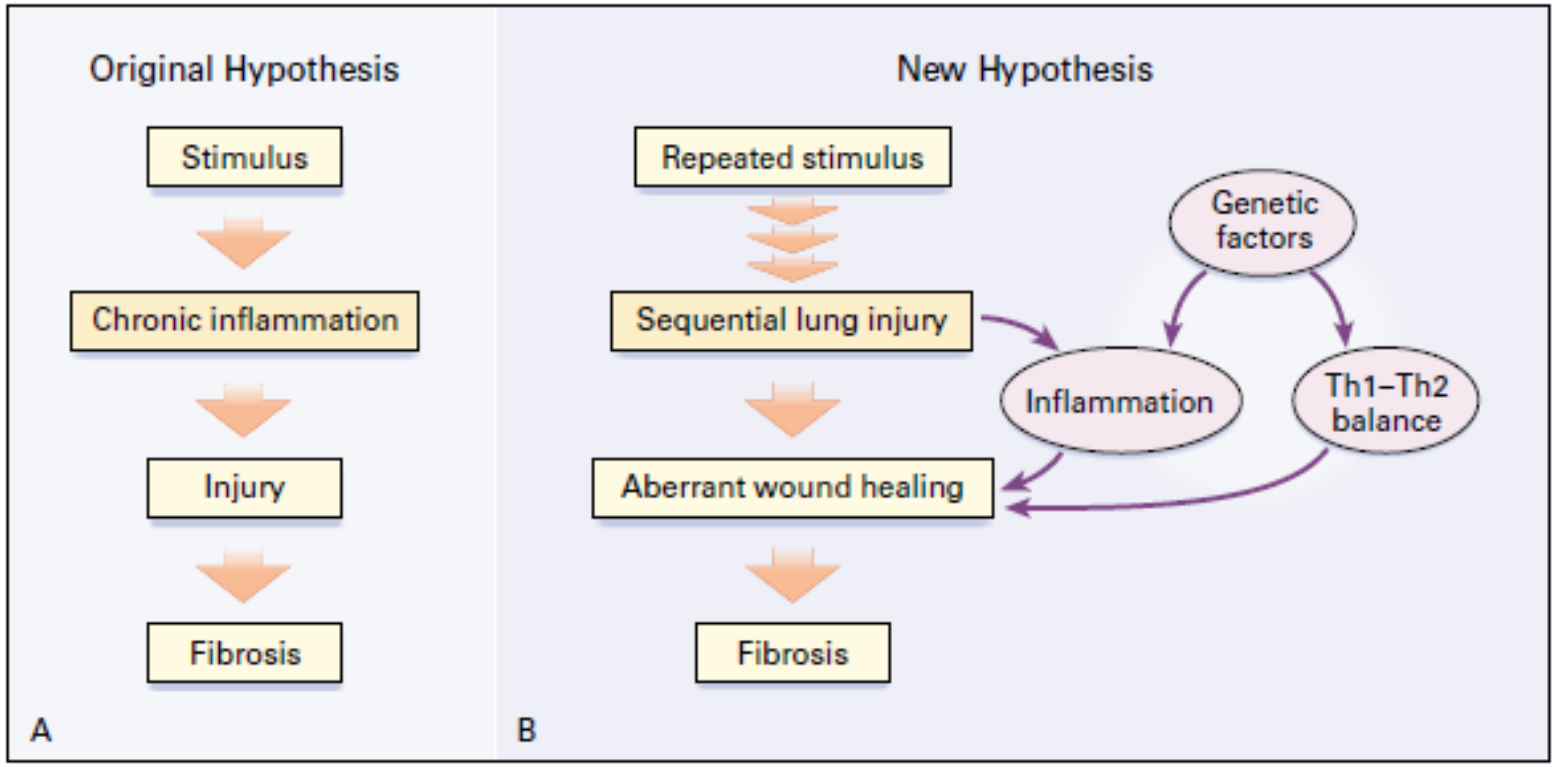
PANTHER Study – Pred/Aza/NAC vs. NAC vs. Placebo

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



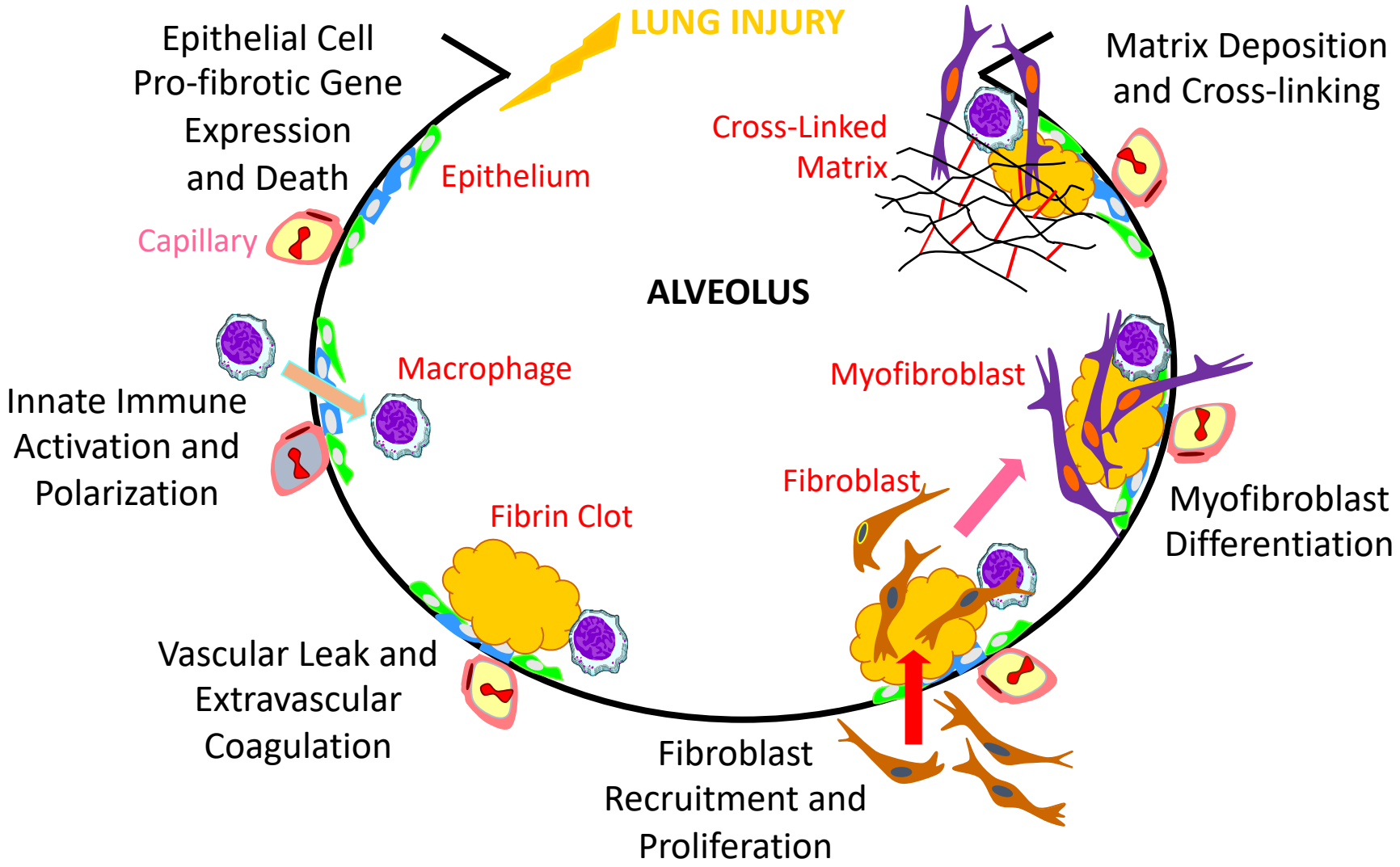
IPFNet. *NEJM.* 2012;366:1968-1977

IPF Pathogenesis – A Shifting Paradigm



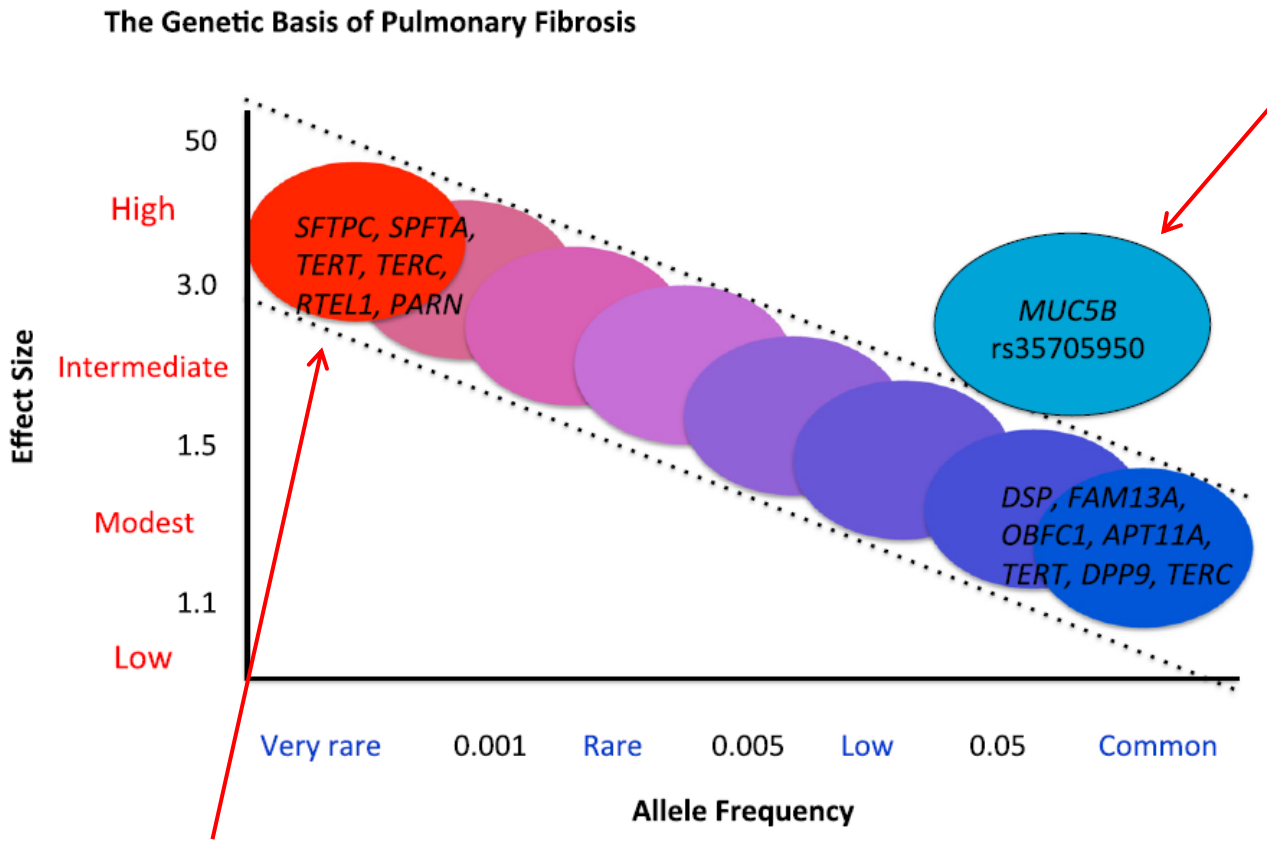
Gross and Hunninghake. *NEJM.* 2001;345(7):517-25

Aberrant Wound-Healing Paradigm of IPF



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

Is IPF a Genetic Disease?



MUC5B polymorphism

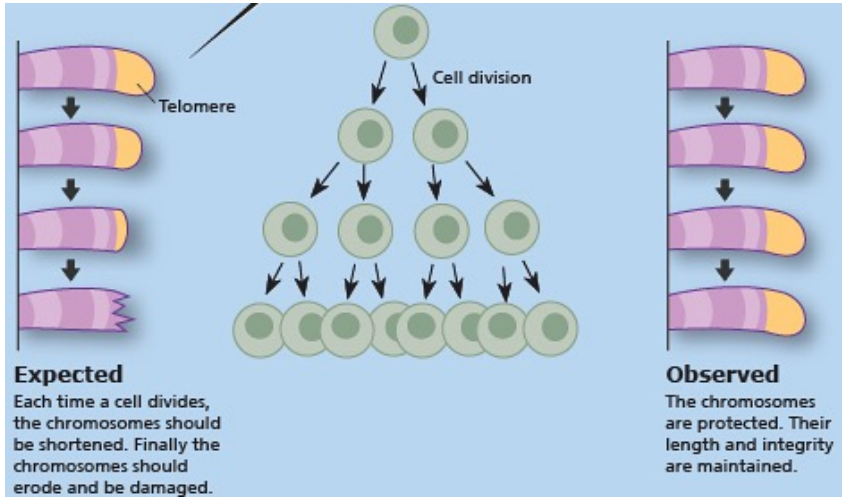
- MAF ~10%
- >5x and >18x risk of IPF with 1 or 2 copies

Rare variants/Medelian inheritance

- Identified in ~20-25% of familial PF

Mathai SK et al. *BMC Med.* 2015.

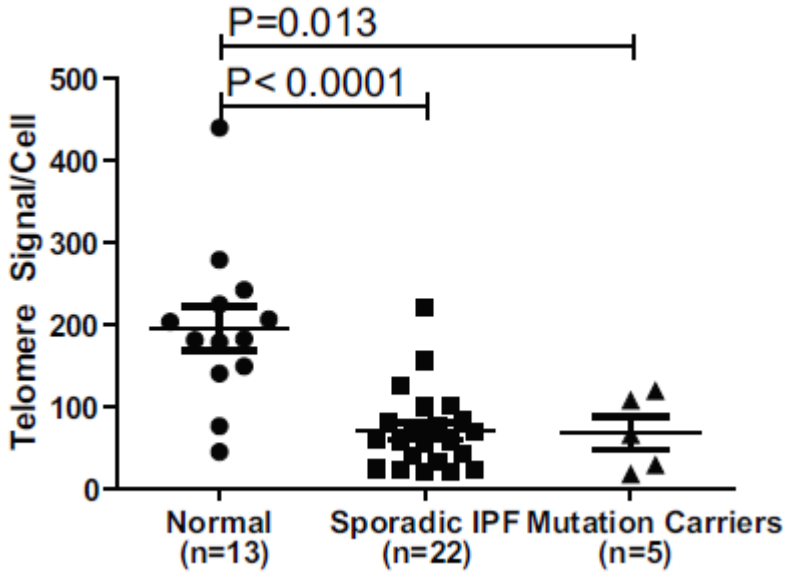
Shortened Telomeres in IPF – a Link to Aging?



www.nobelprize.org; 2009

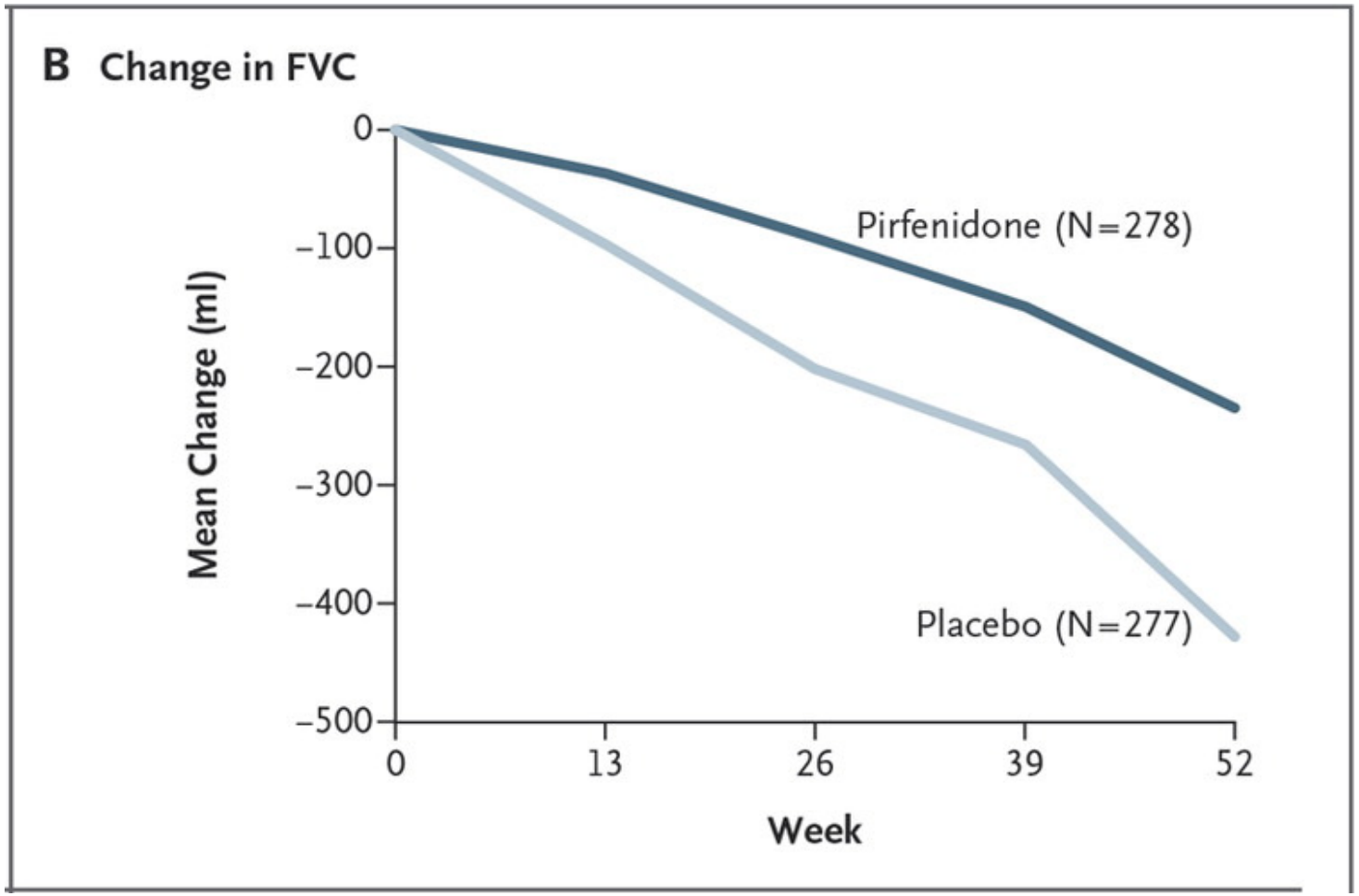
- Pulmonary fibrosis a common feature of dyskeratosis congenita
- *TERT* and *TERC* mutations identified in familial IPF (Tsakiri et al. *PNAS*. 2007;104:7552-7)
- Shortened telomeres in IPF alveolar epithelial cells

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



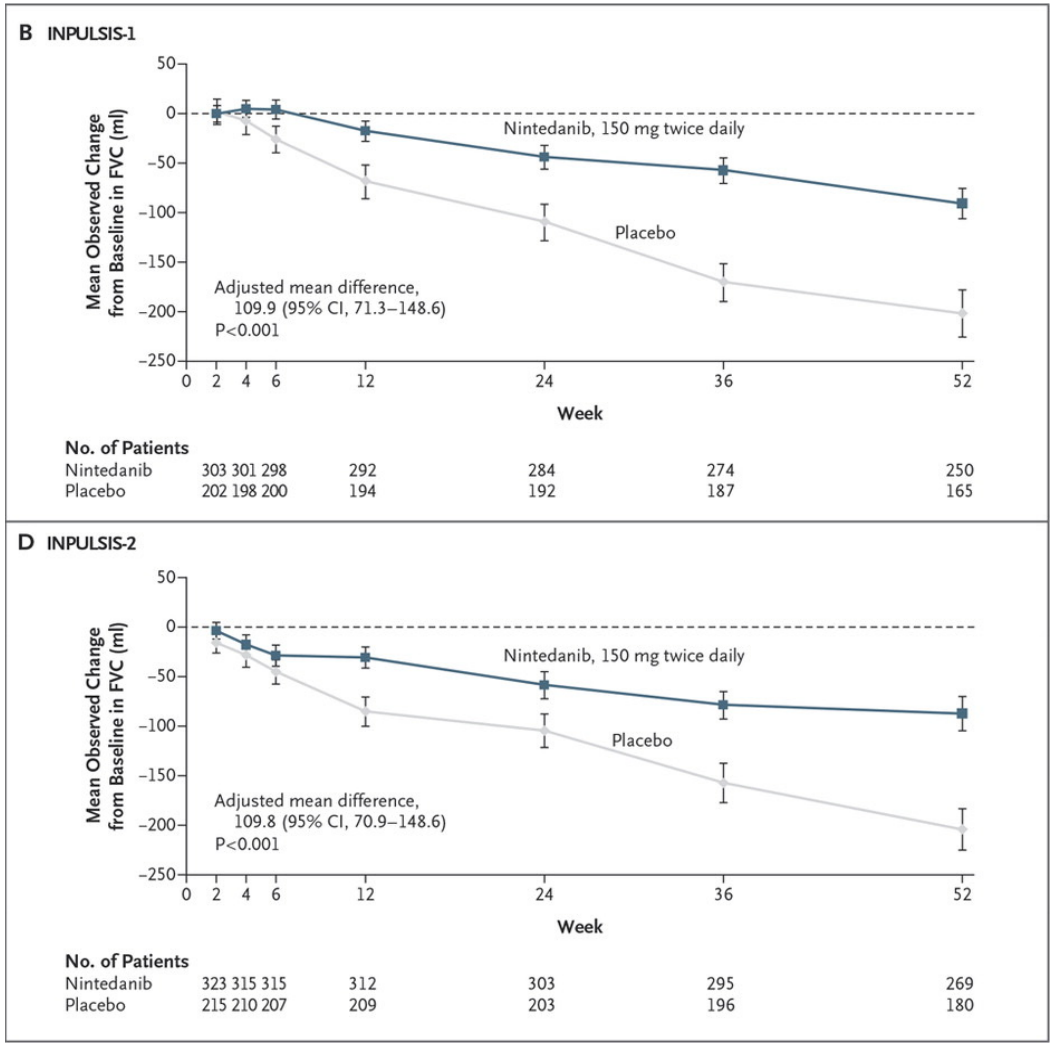
Adler et al. *PNAS.* 2008;105:13051-6

New Therapies for IPF - Pirfenidone



King TE et al. N Engl J Med 2014;370:2083-2092.

New Therapies for IPF – Nintedanib



Richeldi L et al. N Engl J Med 2014;370:2071-2082.

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FDA News Release

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For Immediate Release October 15, 2014

FDA News Release

FDA approves Ofev to treat idiopathic pulmonary fibrosis

For Immediate Release October 15, 2014

Potential PF therapies on the horizon?