

# Interstitial Lung Disease and the Immune System

## Introduction to the iMod.Fc Program

aTyr Pharma Investor and Analyst  
ILD and iMod.Fc Educational Webinar

American Thoracic Society International Conference  
May 23, 2017

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# Agenda

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## **Introduction**

- Mark Johnson, Senior Director Investor Relations, aTyr Pharma

## **Resokine Pathway**

- Sanuj Ravindran, MD, Chief Business Officer, aTyr Pharma

## **ILD Overview**

- Steven Nathan, MD, Director of the Advanced Lung Disease Program and Medical Director of the Lung Transplant Program at Inova Fairfax Hospital, Falls Church, Virginia

## **iMod.Fc Program**

- Sanjay Shukla, MD, MS, Chief Medical Officer, aTyr Pharma

## **Question & Answer Session**

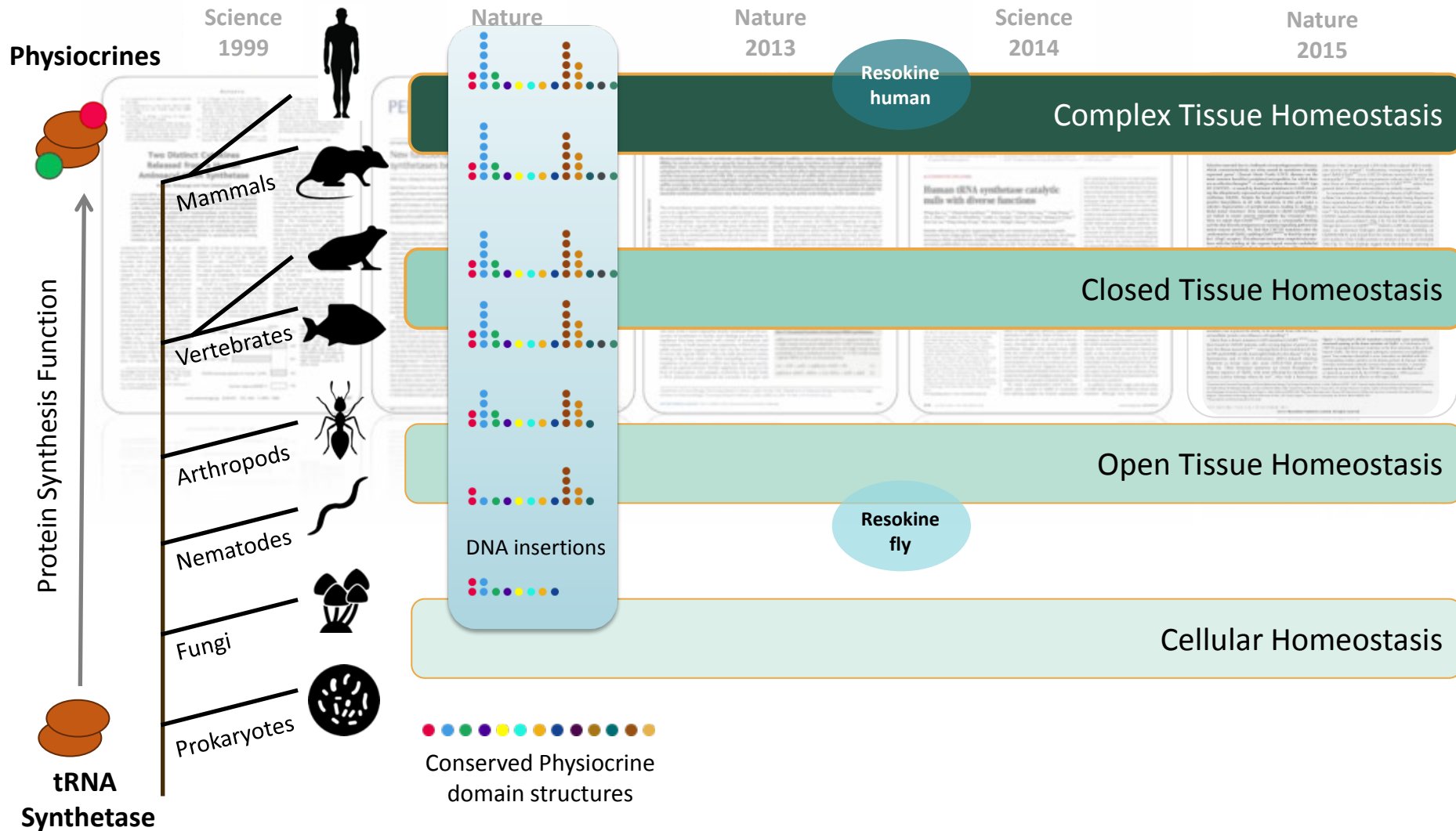


# New Immunological Pathway: Resokine

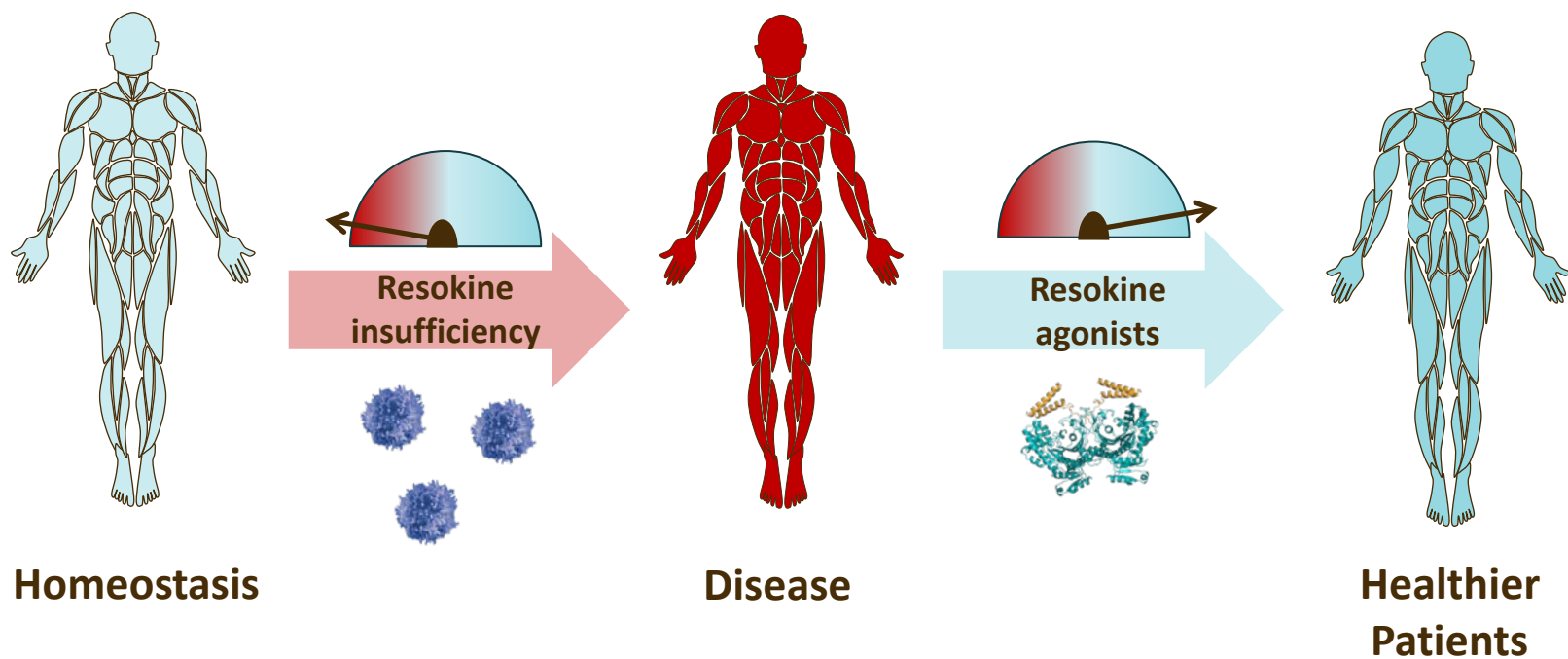
Evolved from Cellular Homeostasis Genes over 400 Million Years

# Resokine: Potential Key Regulator of Homeostasis

*Evolved with System Complexity*



# LIFE's Therapeutic Paradigm

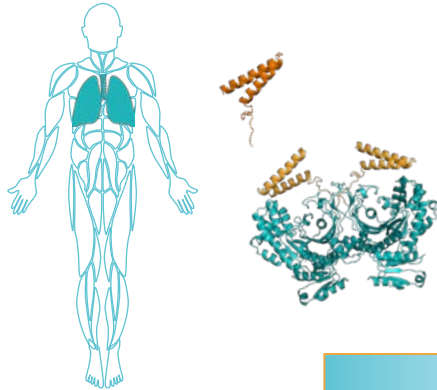




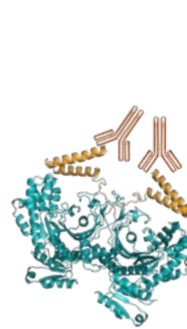
# Disrupting the Resokine Pathway Promotes ILD

*Evidence for Homeostatic Role of Resokine in Humans*

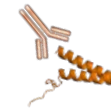
## Homeostasis



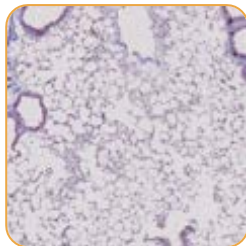
## Imbalance



100% (18 of 18)  
anti-synthetase syndrome  
patients tested positive for  
antibodies for Resokine proteins

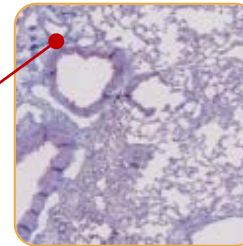


Disease antibodies



Healthy lung

↑ Immune cell  
Invasion / activity

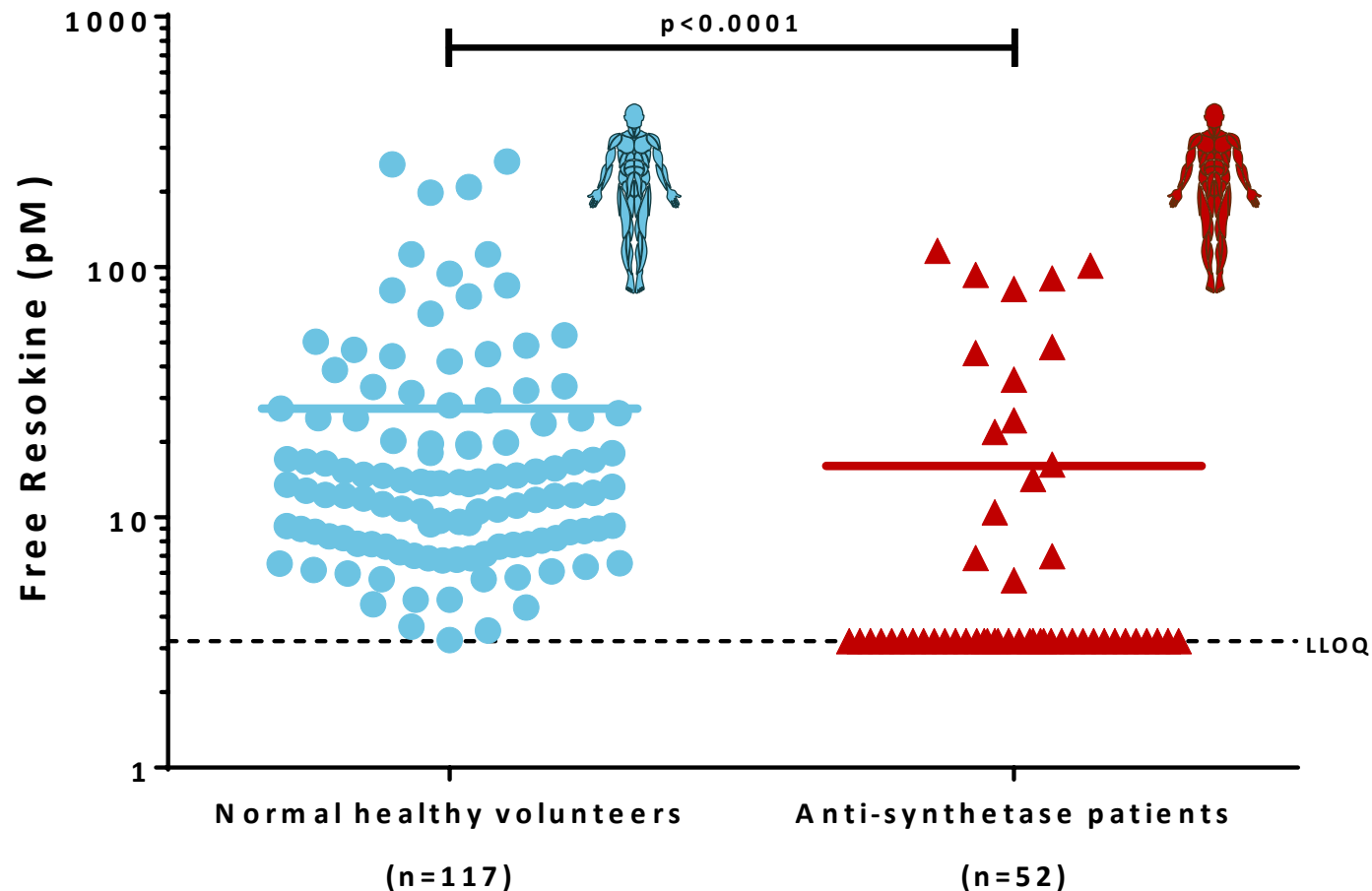


Diseased Lung

## Lung Characteristics

- Increased T cells in BALF
- Decreased CD4/CD8 ratio
- Histology ranges from NSIP to DAD as severity of disease increases

# Free Resokine Pathway in Anti-Synthetase Patients Diminished



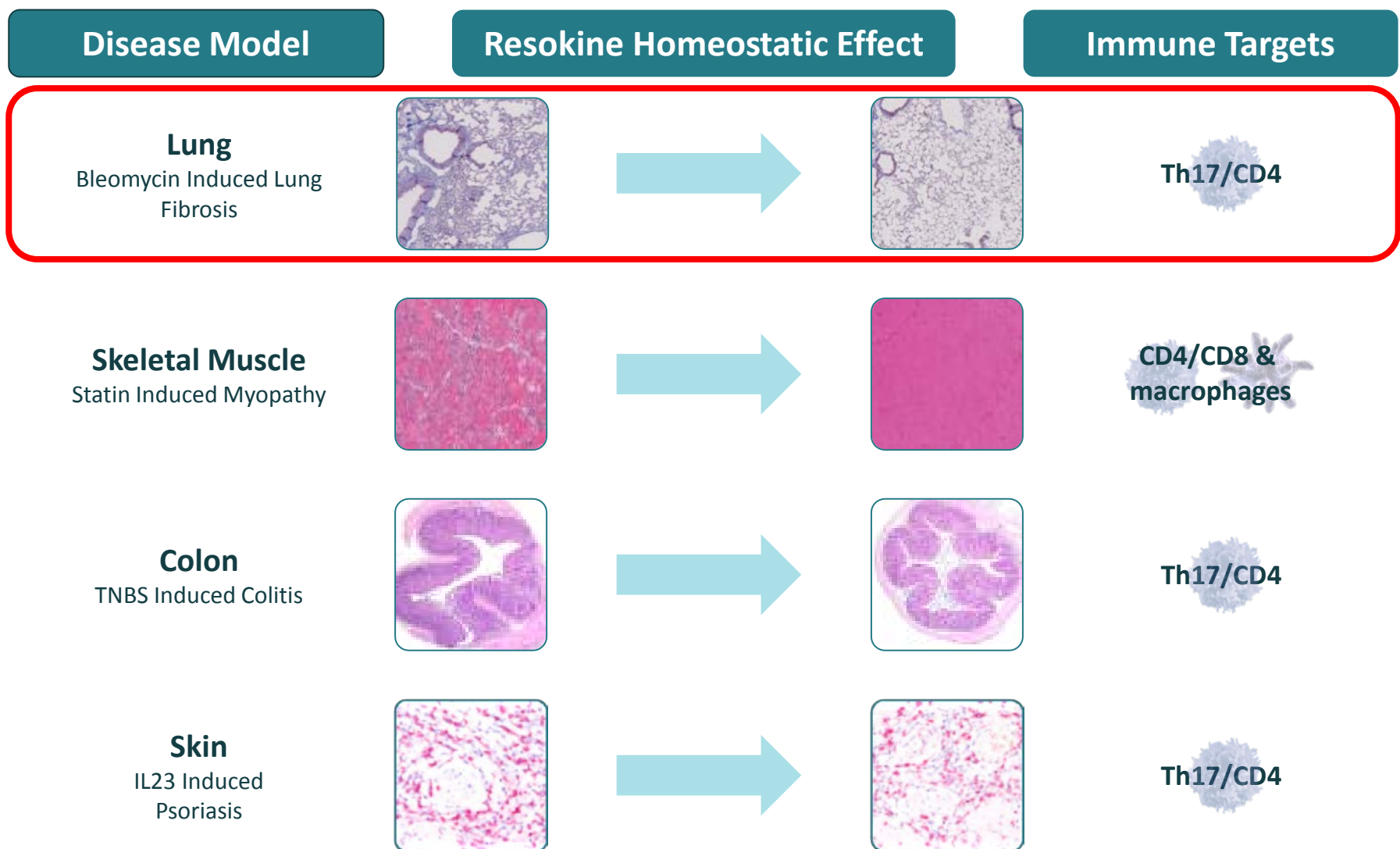
>85% of patients develop Interstitial Lung Disease (ILD)

69% at or below limit of detection



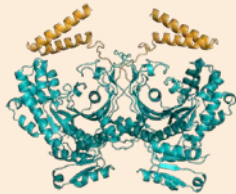
# Agonists of the Resokine Pathway in Immune Driven Models

*Balancing the immune response to tissue insults*



# Three Distinct Therapeutic Modalities Harnessing Knowledge of New Immunological Pathways

## Resolaris



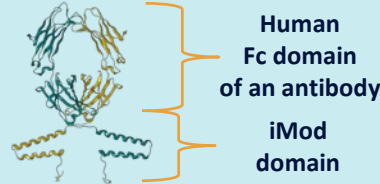
Recombinant version of naturally occurring **Resokine**

**Indications:** Rare muscular dystrophies characterized by immune cell infiltration

**Clinical data** in multiple rare muscular dystrophies

**Generally favorable safety** profile in 44 patients dosed to date

## iMod.Fc



Engineered fusion protein with Resokine splice variant (**iMod**)

**Human Fc domain:** increased exposure to potentially enable **TPP = once monthly dosing**

**Indications:** Rare ILDs characterized by immune cell infiltration

**Preclinical activity** in industry proven model of IPF (approved drugs Pirfenidone & Nintedanib)

## ORCA



3<sup>rd</sup> therapeutic modality

**Biologics program** based on aTyr's knowledge of new pathways in immunology

**Preclinical activity** to identify IND candidate in 2017

# Overview of Interstitial Lung Disease

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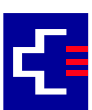
Steven Nathan, MD

Medical Director,

Advanced Lung Disease & Transplant Program

Inova Fairfax Hospital

Falls Church, Virginia USA

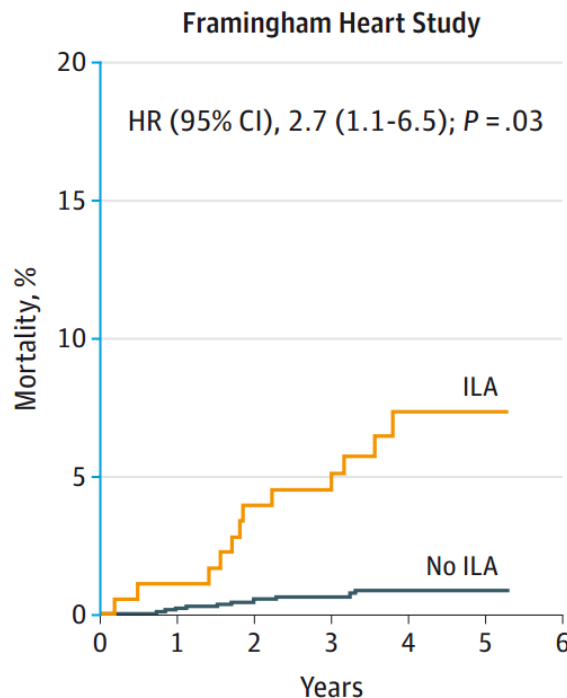


# Disclosures: Steven Nathan, MD

## Personal financial relationships with commercial interests relevant to this presentation during the past 12 months:

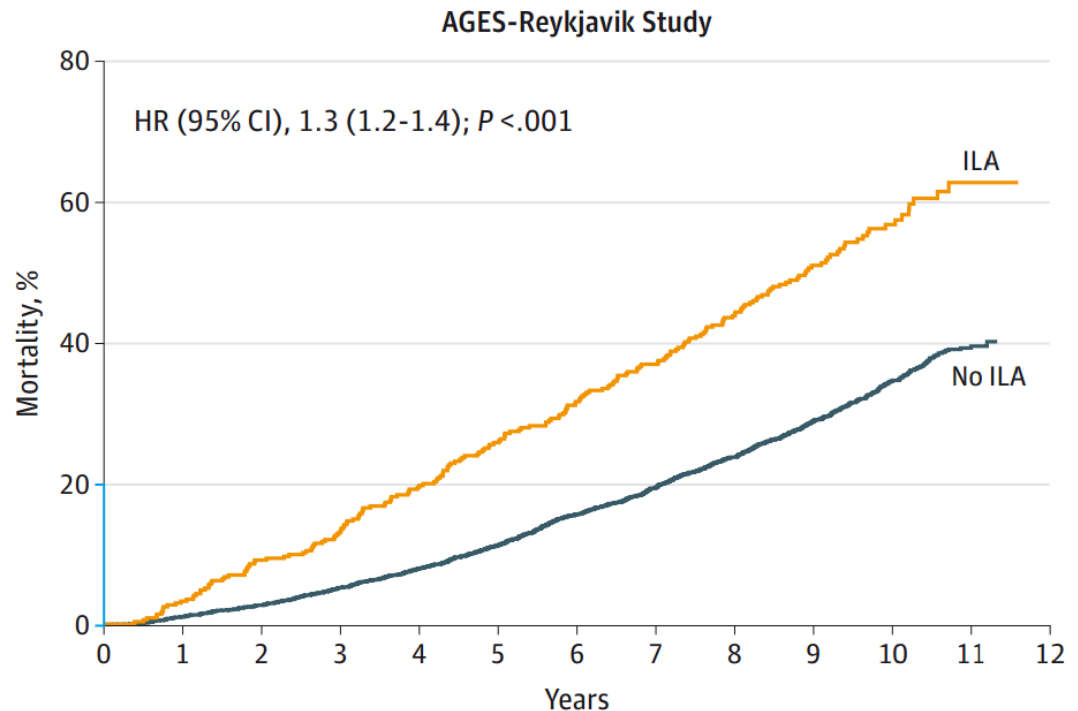
- ❖ **Consultant:** aTyr Pharma, Bayer Pharmaceuticals, Boehringer-Ingelheim, Genentech-Roche, Gilead, Third Pole, United Therapeutics.
- ❖ **Speaker's Bureau:** Bayer, Boehringer-Ingelheim, Genentech, Gilead, Grifols, United Therapeutics.
- ❖ **Research Funding:** Actelion, Bayer, Boehringer-Ingelheim, Gilead, Genentech-Roche, United Therapeutics, Veracyte.

# Association between Interstitial Lung Abnormalities and All-cause Mortality



No. at risk

ILA	177	176	171	170	107
No ILA	1370	1367	1364	1361	1022



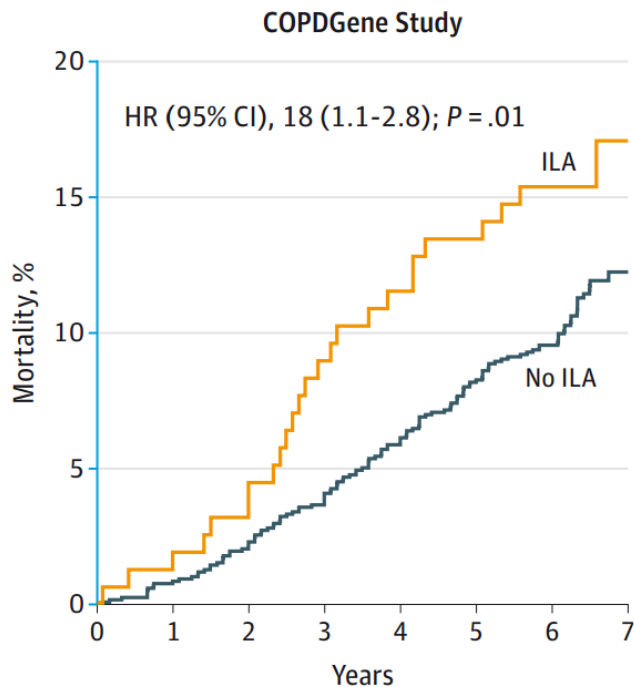
No. at risk

ILA	378	365	343	328	304	281	259	239	213	137	68	12
No ILA	3216	3177	3124	3044	2956	2851	2710	2589	2447	1694	862	228

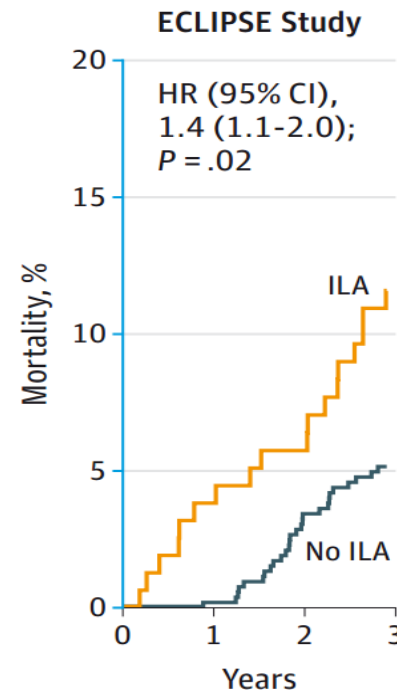
Blue segments of y-axes indicate mortality range from 0% to 20%. P values included in each panel are associated with hazard ratios (HRs [95% CIs]) from the adjusted Cox proportional hazards model including adjustments for age, sex, race, body mass index, pack-years of smoking, current or former smoking status, and GOLD stage of COPD (except in AGES-Reykjavik where GOLD stage was not available). AGES indicates the Age Gene/Environment Susceptibility.

JAMA 2016;315:672-681

# Association between Interstitial Lung Abnormalities and All-cause Mortality



No. at risk							
ILA	156	153	149	142	138	135	131
No ILA	1173	1163	1146	1125	1104	1079	1062



No. at risk			
ILA	156	151	145
No ILA	528	525	505

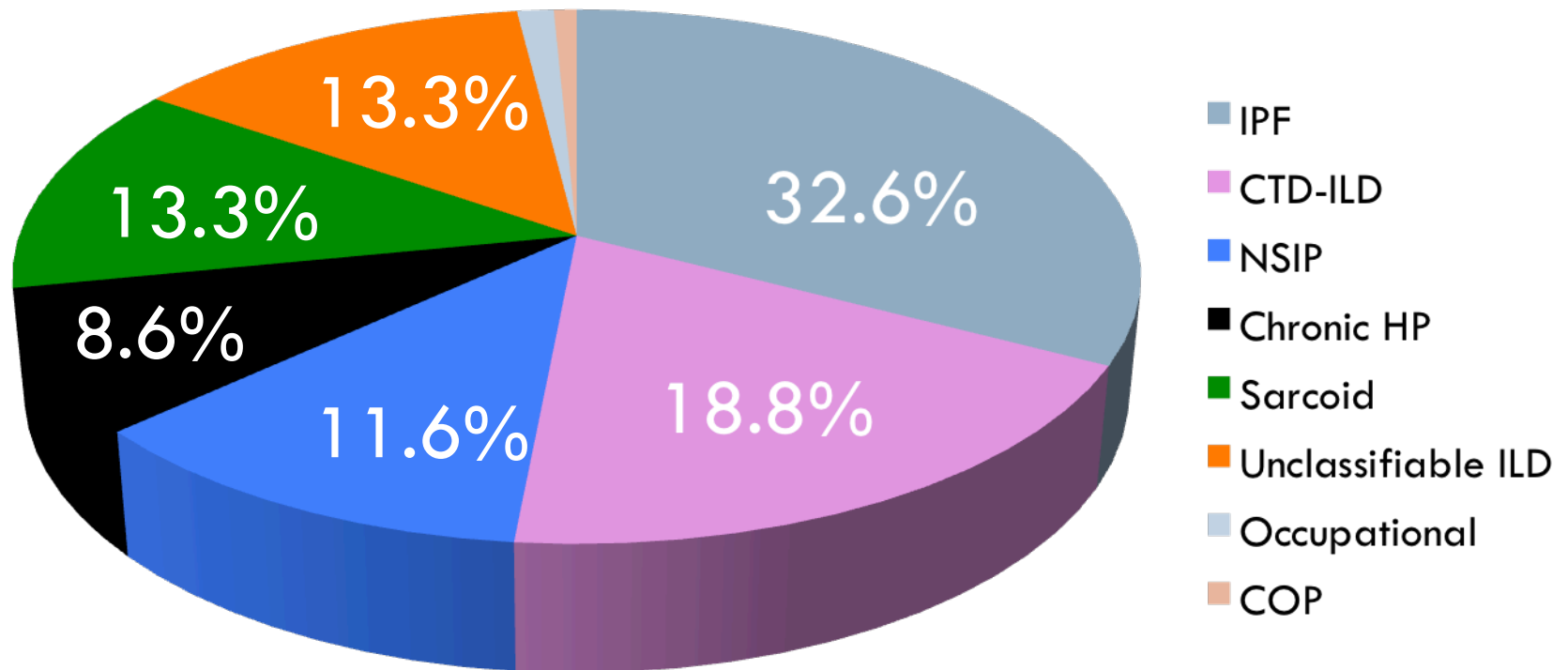
Blue segments of y-axes indicate mortality range from 0% to 20%. P values included in each panel are associated with hazard ratios (HRs [95% CIs]) from the adjusted Cox proportional hazards model including adjustments for age, sex, race, body mass index, pack-years of smoking, current or former smoking status, and GOLD stage of COPD. COPD, chronic obstructive pulmonary disease; ECLIPSE, Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ILA, interstitial lung abnormalities.

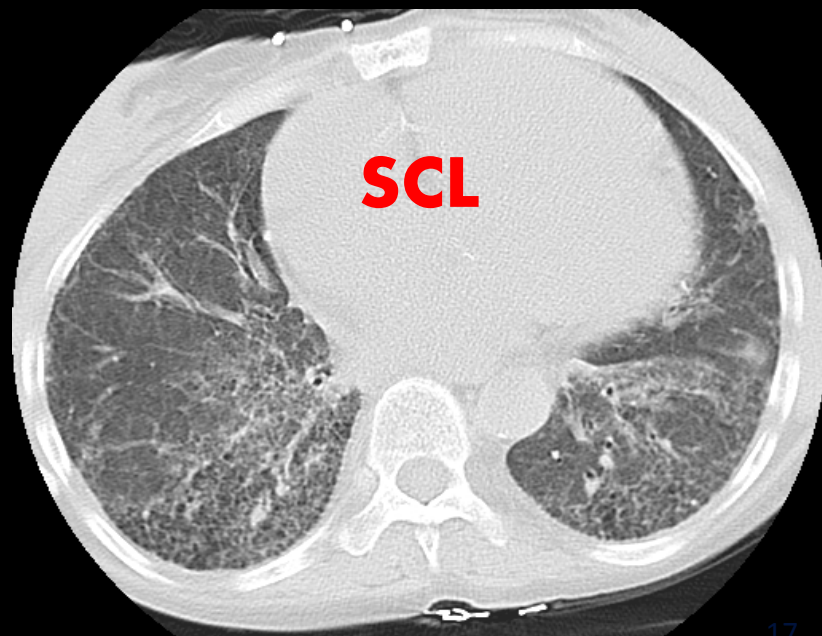
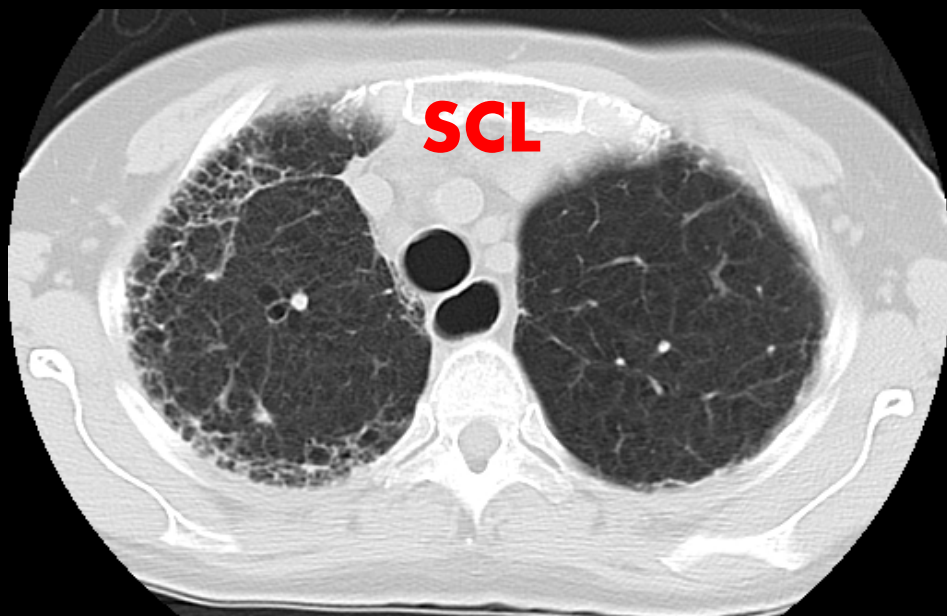
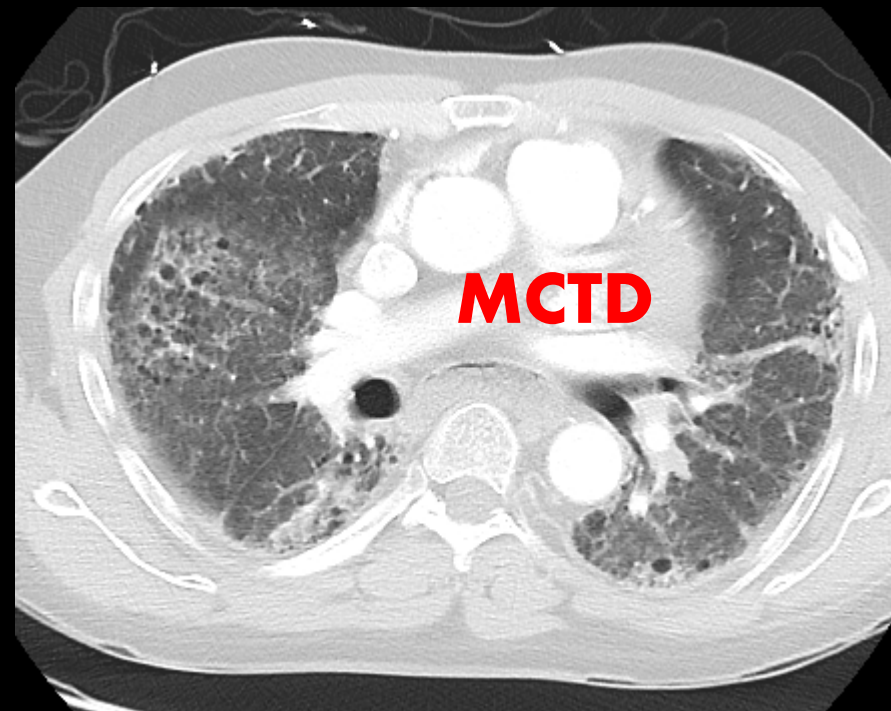
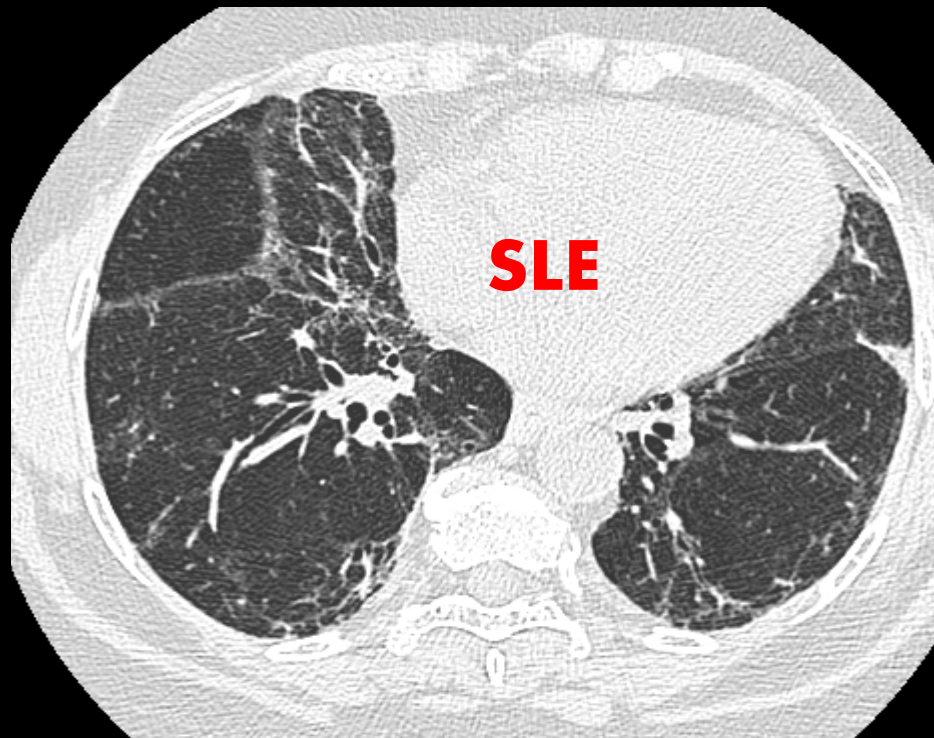
JAMA 2016;315:672-681



Category	Diseases	Sub-categories/examples	Inflammation	Fibrosis
Idiopathic	Idiopathic Interstitial Pneumonias (IIPs)	IPF	+/-	+++
		NSIP	+	++
	Sarcoidosis	Unclassifiable	+++	+++
	Amyloidosis	COP	++	+
		RB-ILD	++	-
	Lymphangiomyomatosis	DIP	++	+
		AIP	+/-	+
	PLCH, Eosinophilic pneumonia. Neurofibromatosis, DAH	LIP PPFE	+++ -	- +++
Immunologic	Connective Tissue Disorders		++	++
Inhalational	Inorganic	Asbestosis, Silicosis	-	++
	Organic: Chronic hypersensitivity pneumonitis	Bird fanciers disease, Farmer's lung	++	+
Iatrogenic	Antiarrhythmics Antimicrobials Chemotherapy agents Biologics  Radiation		-	+
Infectious	Viral	CMV, influenza	N/A	N/A
	Fungal	Pneumocystis carinii	N/A	N/A
Chronic CHF			N/A	N/A
Neoplastic	Lymphangitic carcinomatosis Bronchoalveolar carcinoma		N/A	N/A

# Spectrum of ILD followed by Inova ALD Program (N=657)

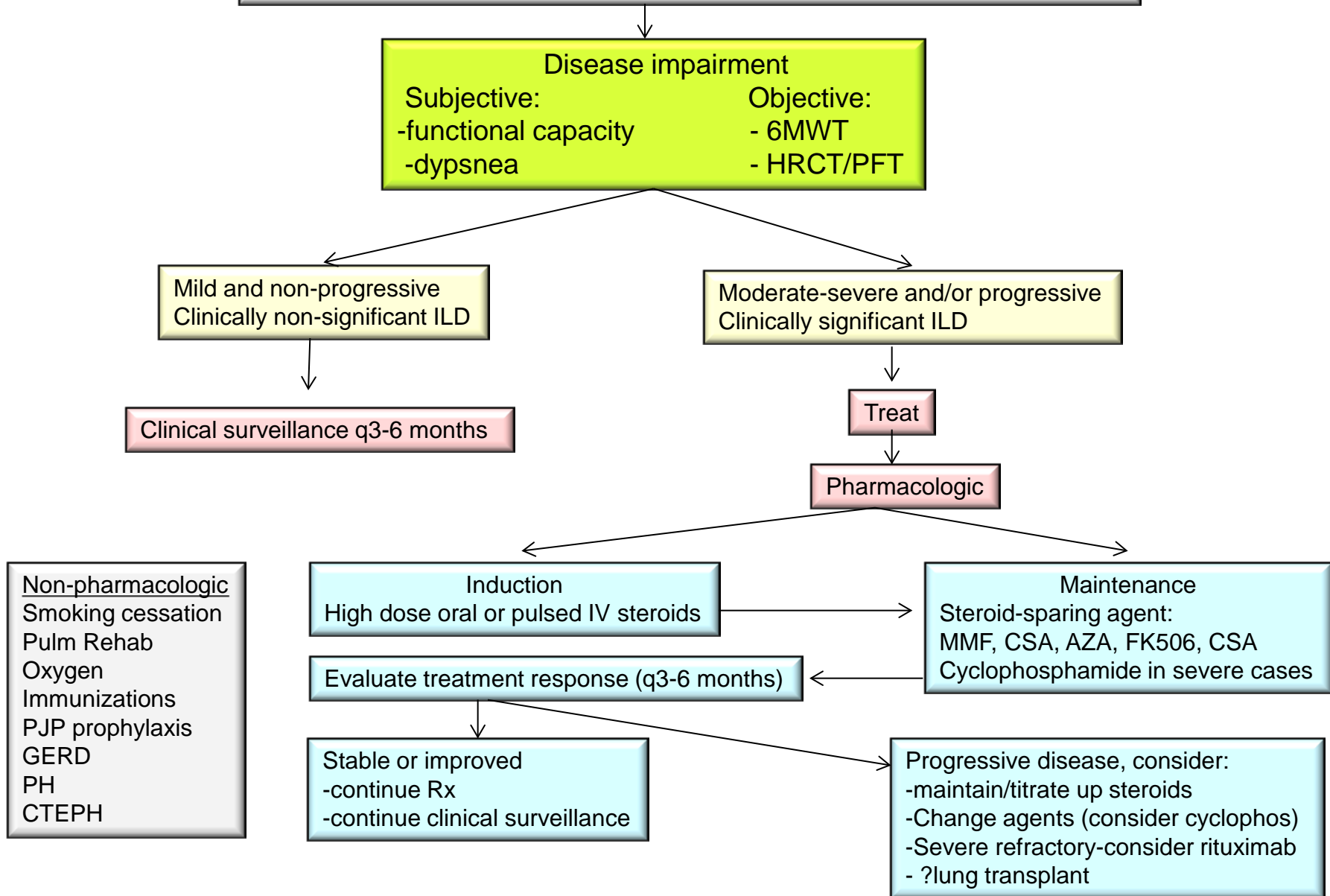




# Prevalence of ILD in CTD

- 1,600 deaths in USA annually
  - ▣ 25% of all ILD deaths
  - ▣ 2% of respiratory deaths
- RA: 15-20%
- PM/DM: 5-20%
- SLE: 5-18%
- Scleroderma: 50-70%
- Sjogrens: 5-40%

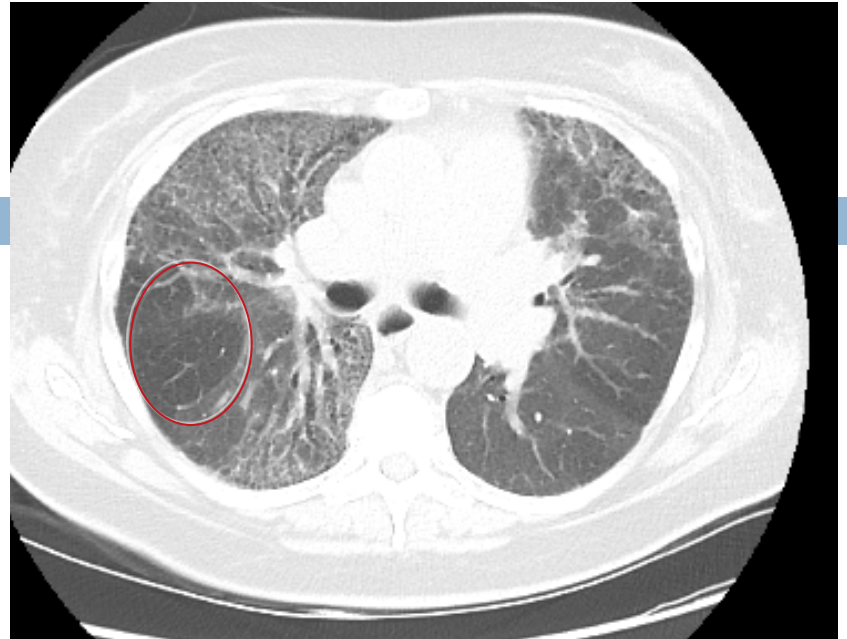
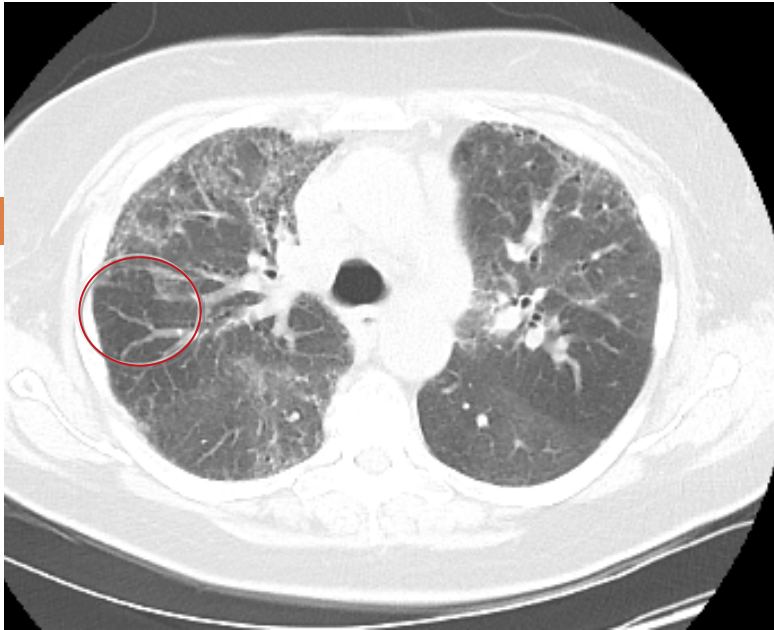
# APPROACH TO THE TREATMENT OF CTD-ILD



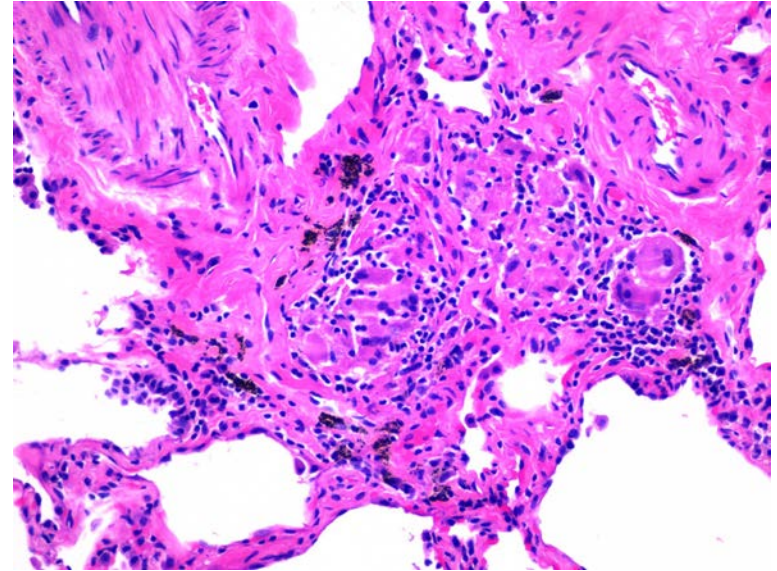
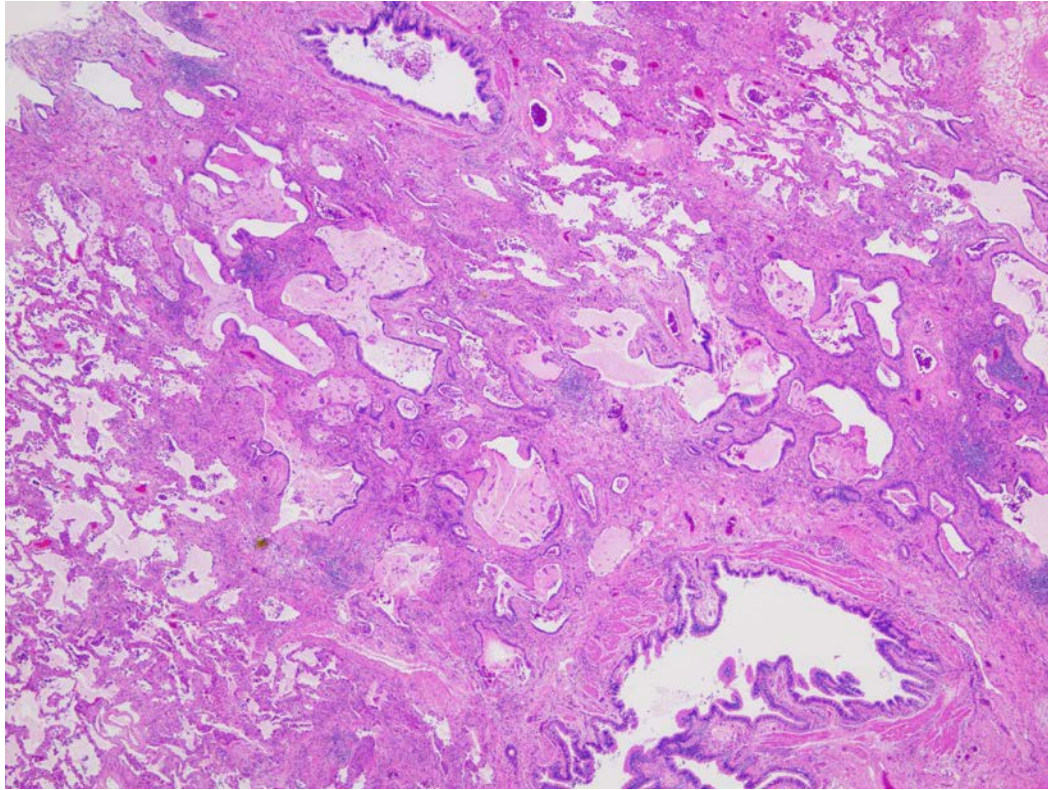
# Chronic Hypersensitivity Pneumonitis

- Birds, hot tubs, mold, “idiopathic”
- Insidious in onset
- May mimic UIP
- Utility of HP panel uncertain
- Inspiratory and expiratory CT
  - ▣ - air-trapping or “mosaism”





# Chronic HP: Pathology

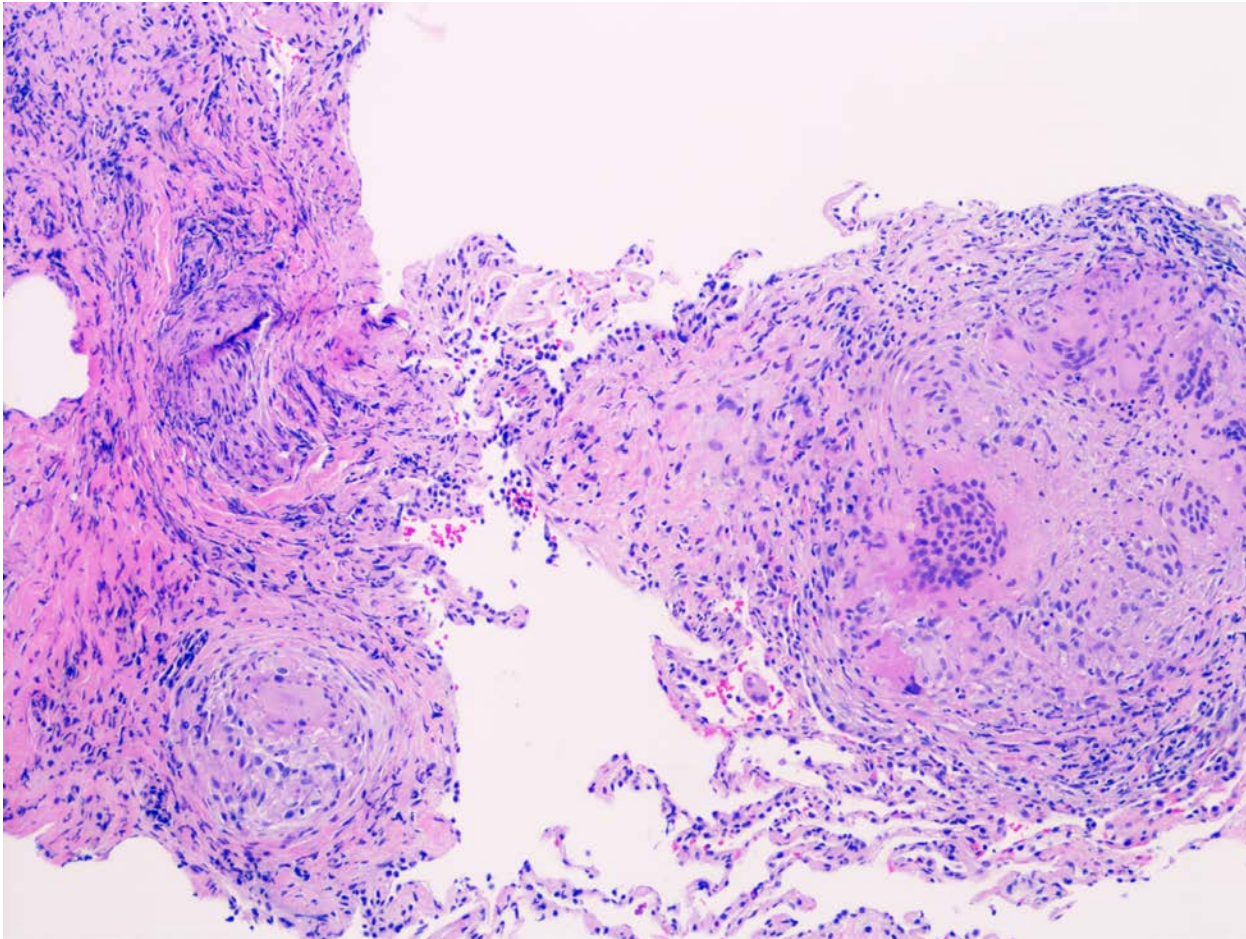


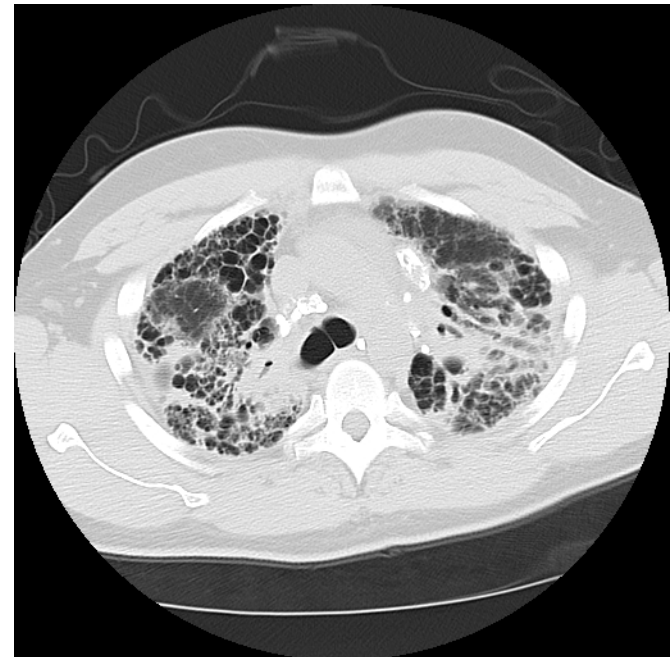
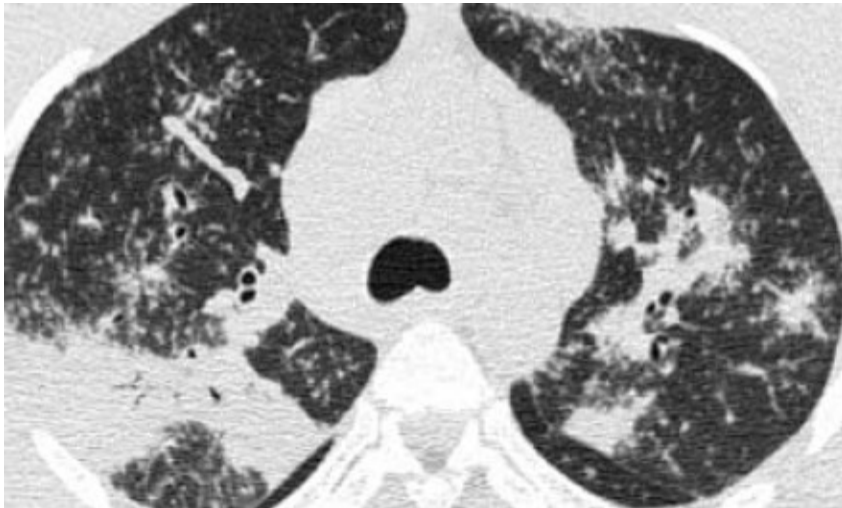
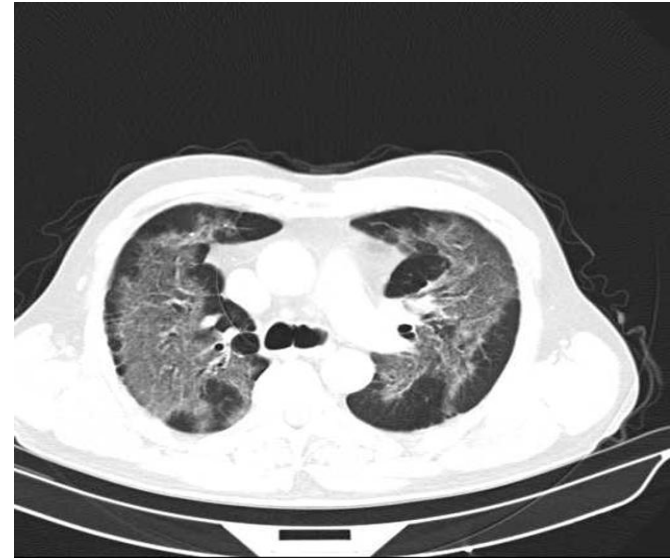
# Sarcoidosis: Systemic Disease

- A multisystem disease
  - Unknown etiology
  - Granulomatous disorder
  - Affects individuals world wide
  - Most often affects young adults
- Prevalence of 10-20 per 100,000 population
- Incidence is unknown
  - Varies among geographical groups
  - Lifetime incidence in blacks is 2.4%, in whites 0.85%



# Non-Caseating Granulomas





# Treatment of Sarcoidosis

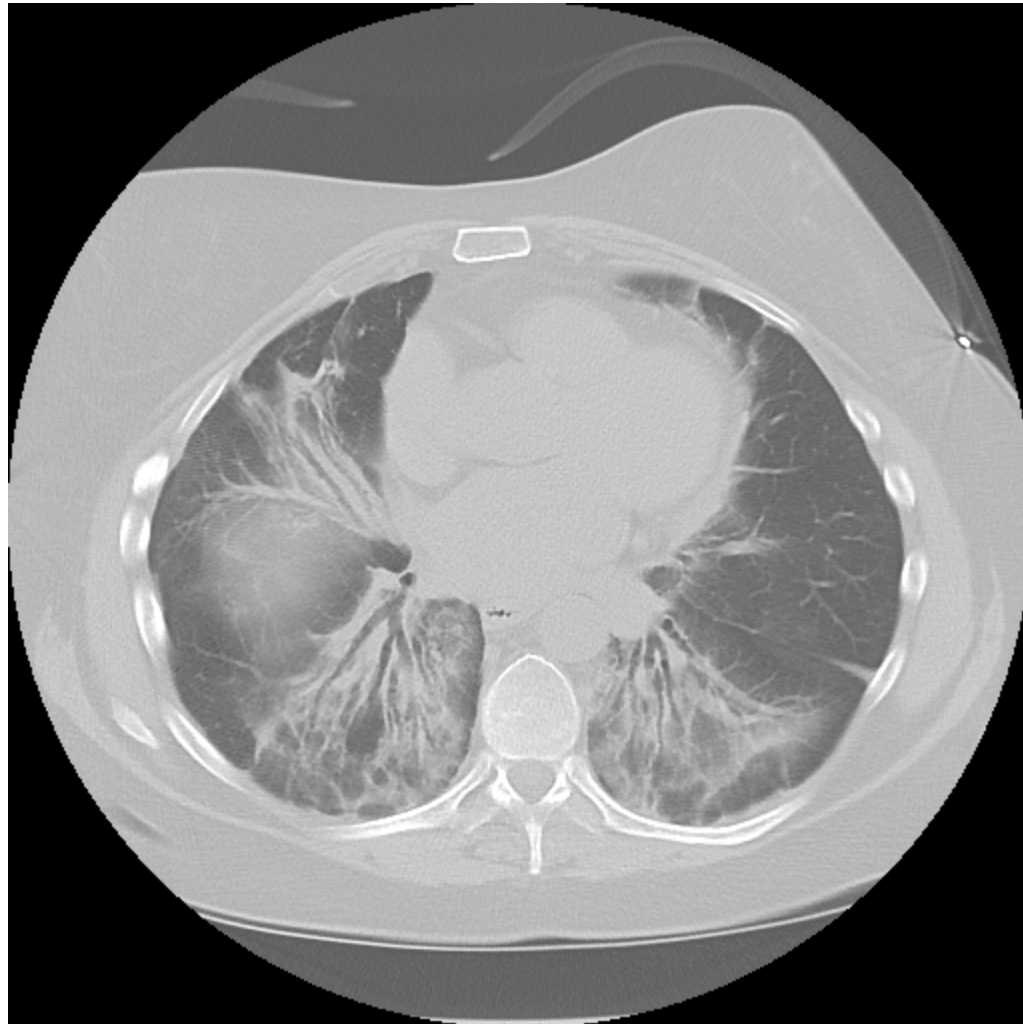
- Not all patients require therapy for sarcoidosis
  - About half never get treated
    - Pulmonary, ocular, neuro, cardiac, hypercalcemia
- Treatment strategies are different based on phase of disease
  - Acute
  - Chronic
  - Refractory
  - Steroids, methotrexate, azathioprine, mycophenolate, leflunomide, infliximab, acthar gel



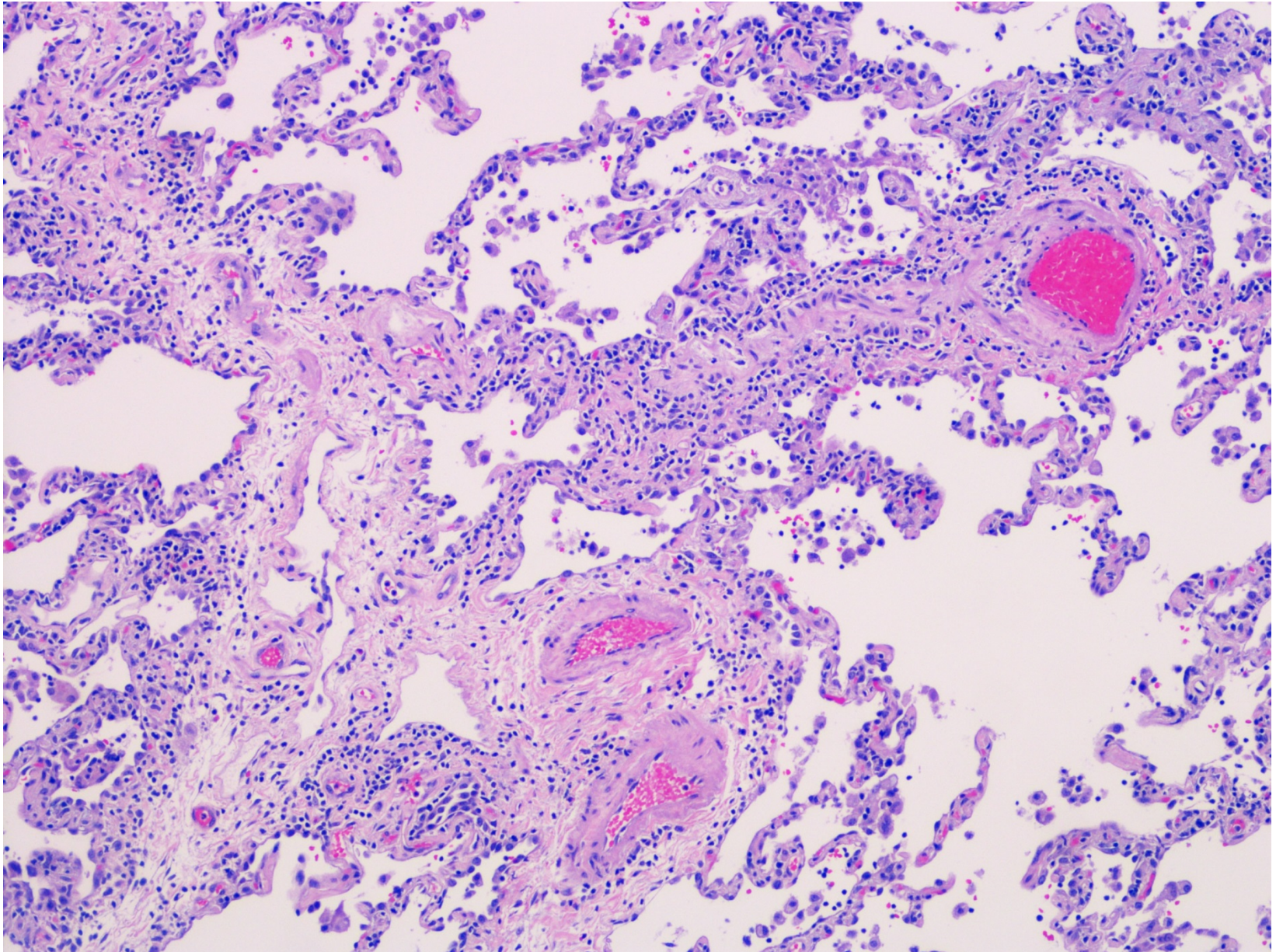
# Revised ATS/ERS Idiopathic Interstitial Pneumonia Classification

<b>Major Idiopathic Interstitial Pneumonias</b>
Idiopathic Pulmonary Fibrosis
Idiopathic nonspecific interstitial pneumonia
Respiratory bronchiolitis interstitial lung disease
Desquamative interstitial pneumonia
Cryptogenic organizing pneumonia
Acute interstitial pneumonia
<b>Rare Idiopathic Interstitial Pneumonias</b>
Idiopathic lymphoid interstitial pneumonia
Idiopathic pleuroparenchymal fibroelastosis
<b>Unclassifiable idiopathic interstitial pneumonias</b>

# NSIP

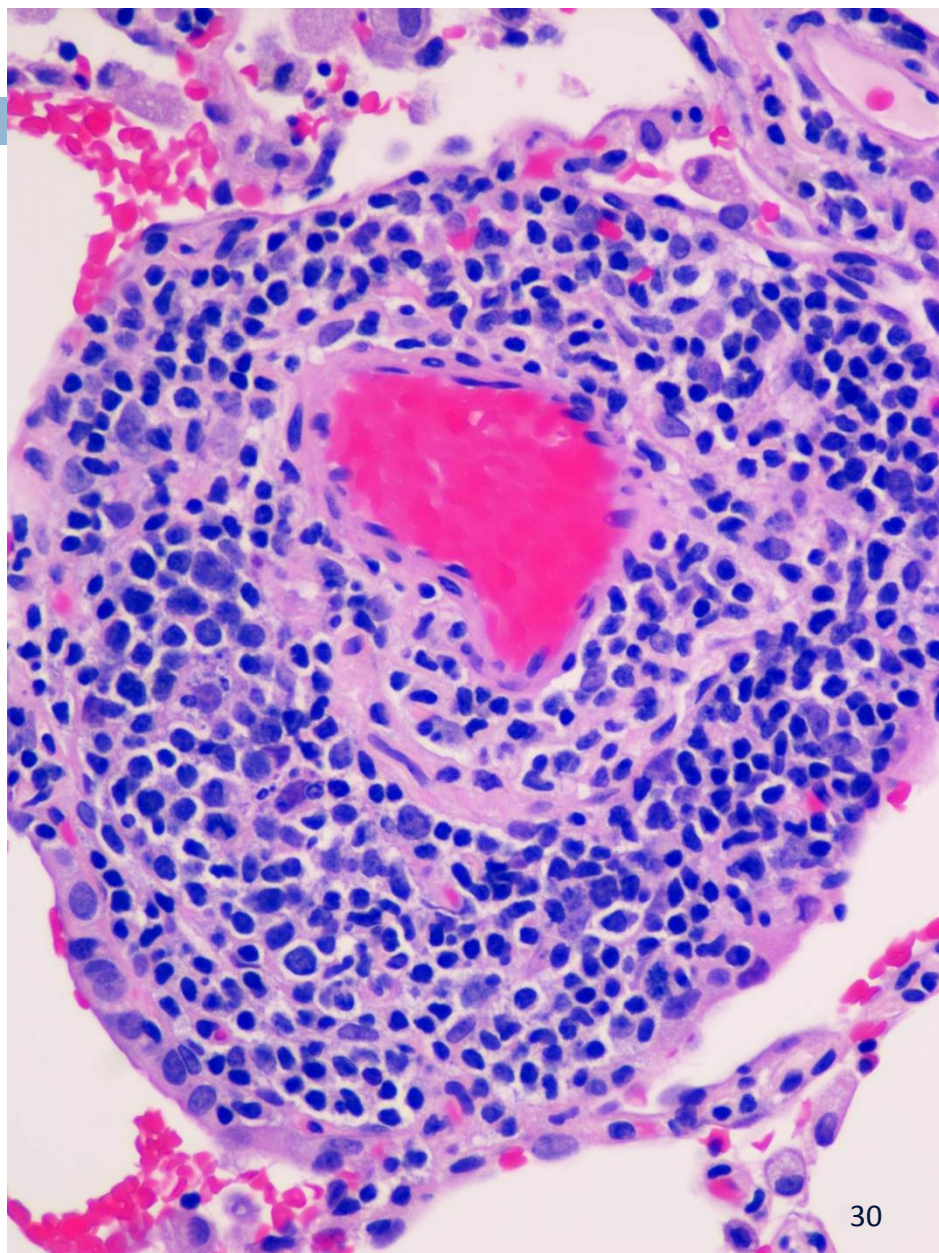
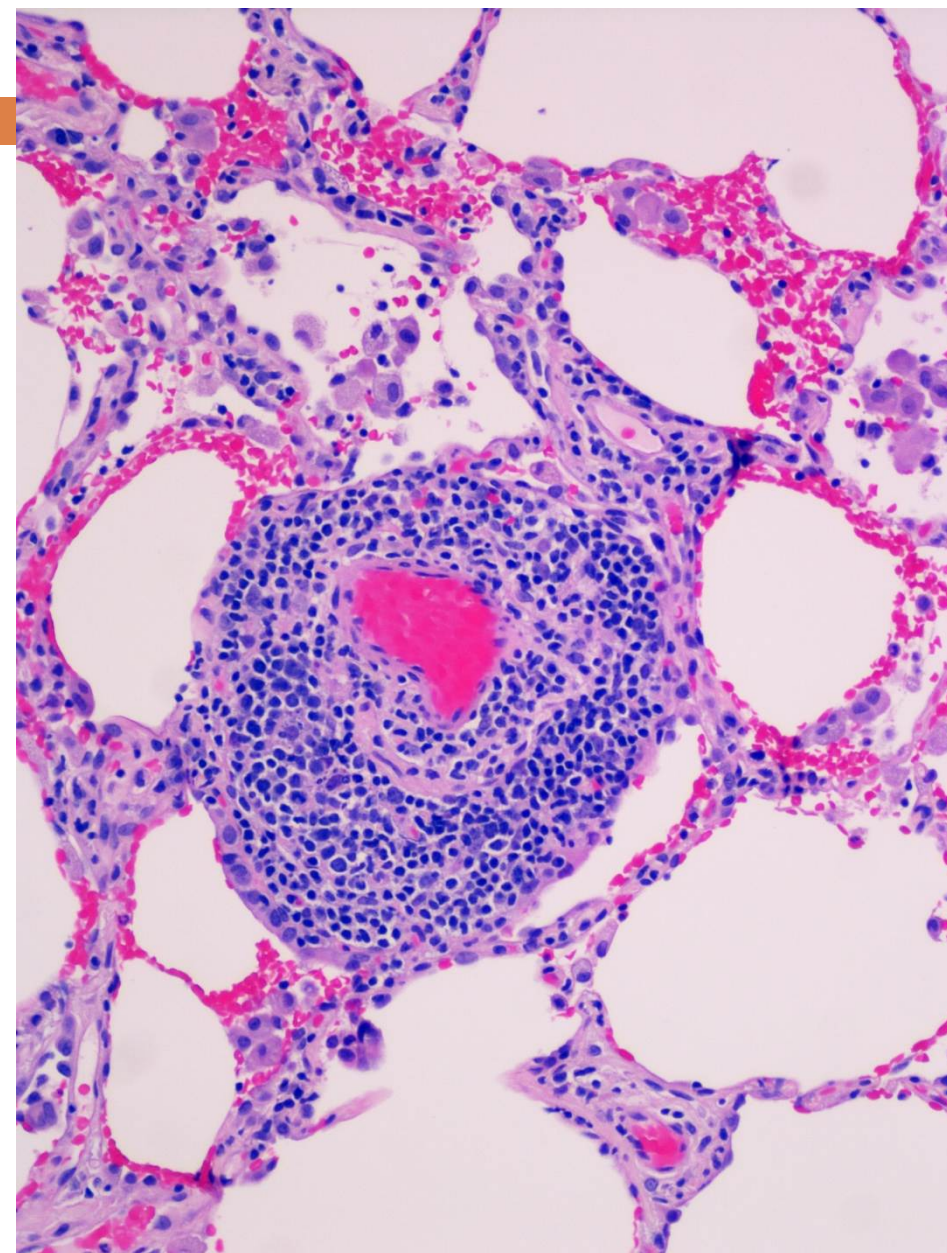


## RML – adjacent mild cellular IP





## RLL – venulitis

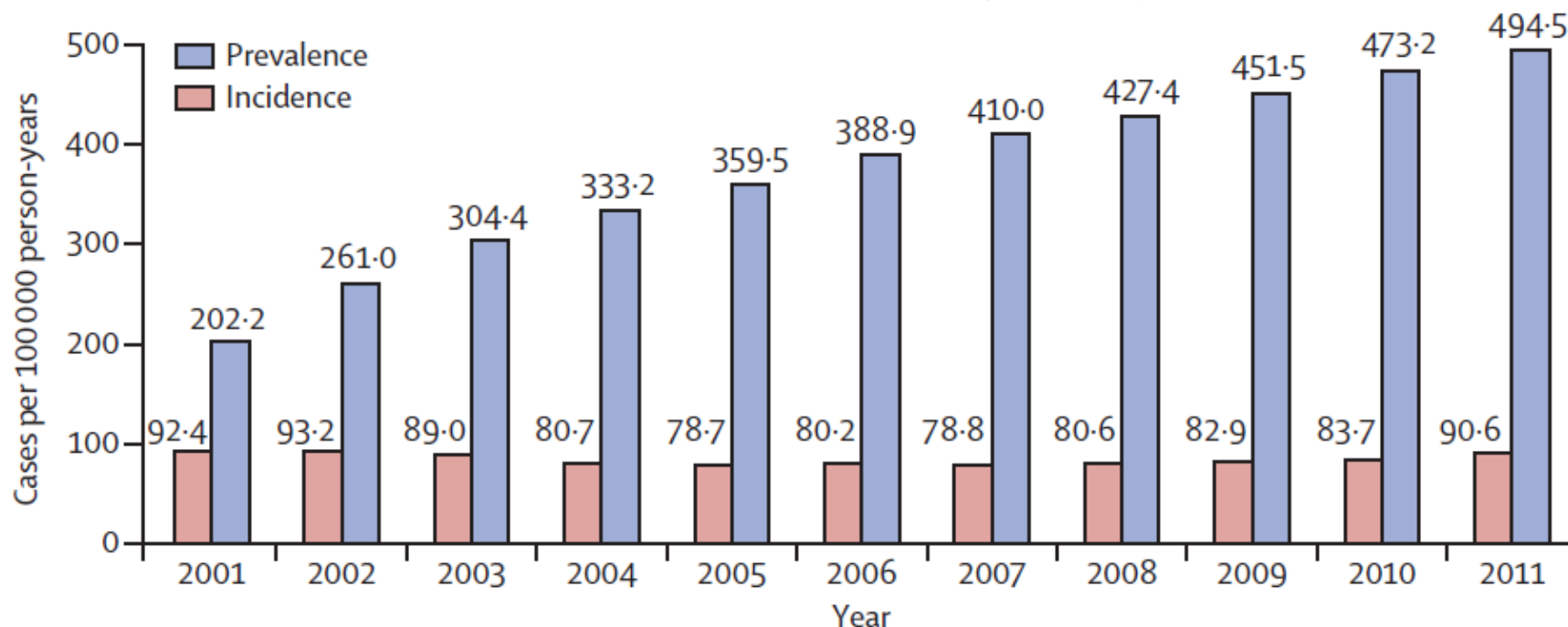


# Current Definition of IPF

- Specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause
- Occurring primarily in older adults
- Limited to the lungs

# Increasing Prevalence of IPF

## Medicare Beneficiaries Age $\geq 65$ y



### Factors associated with lower survival

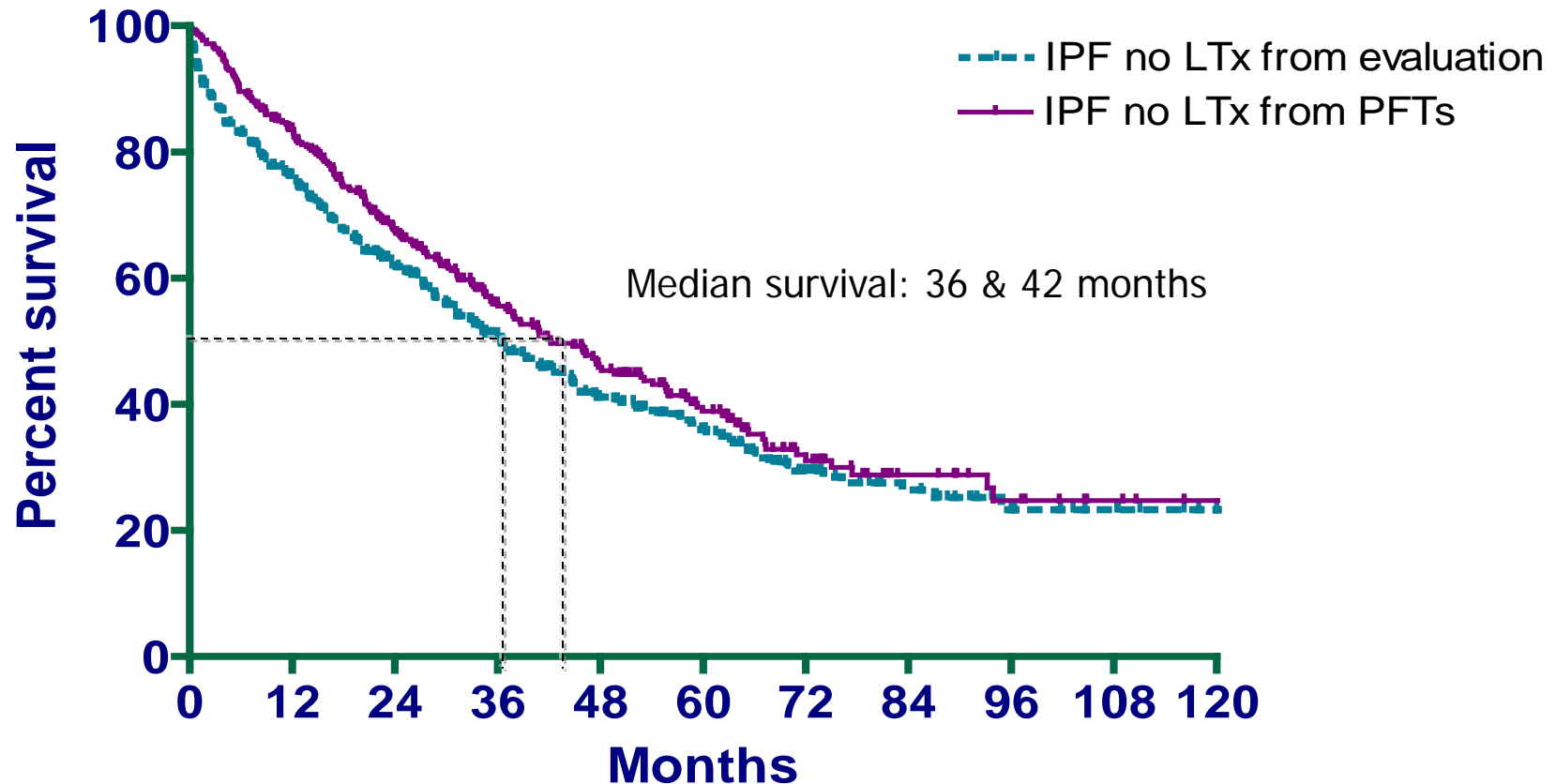
- Age, index year, male gender

Median survival = 3.8 y



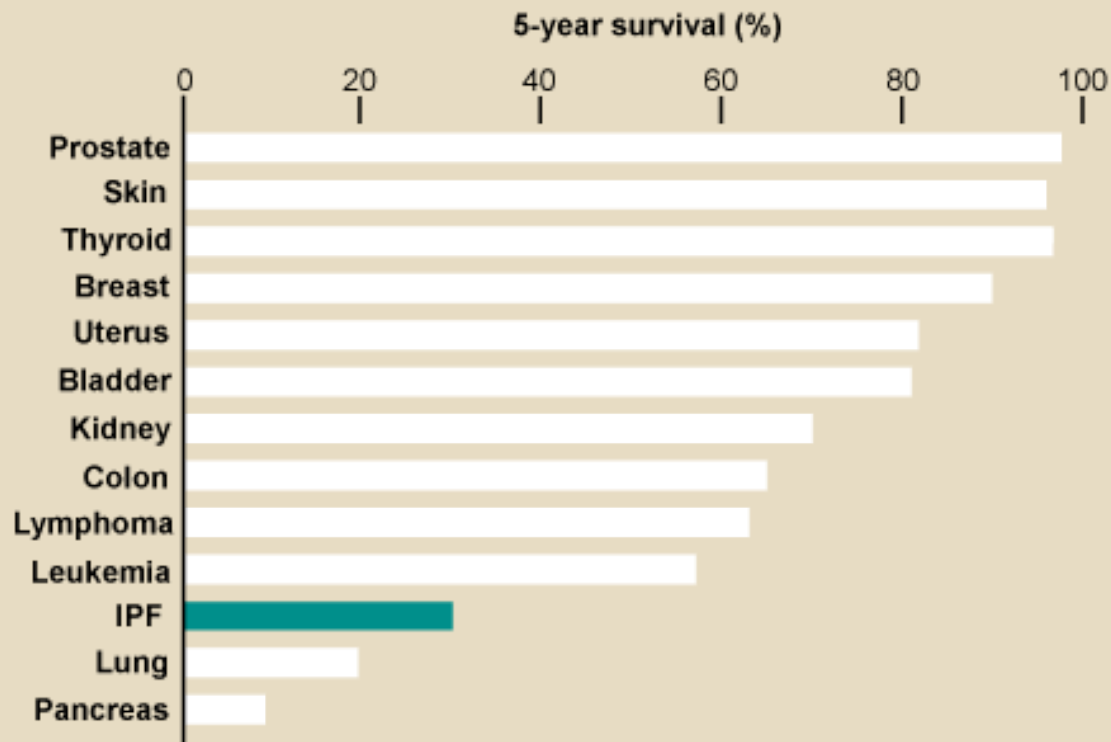
# IPF: Survival at the Turn of the Century

2000-2009 (N=521)



# Mortality Rate High in IPF

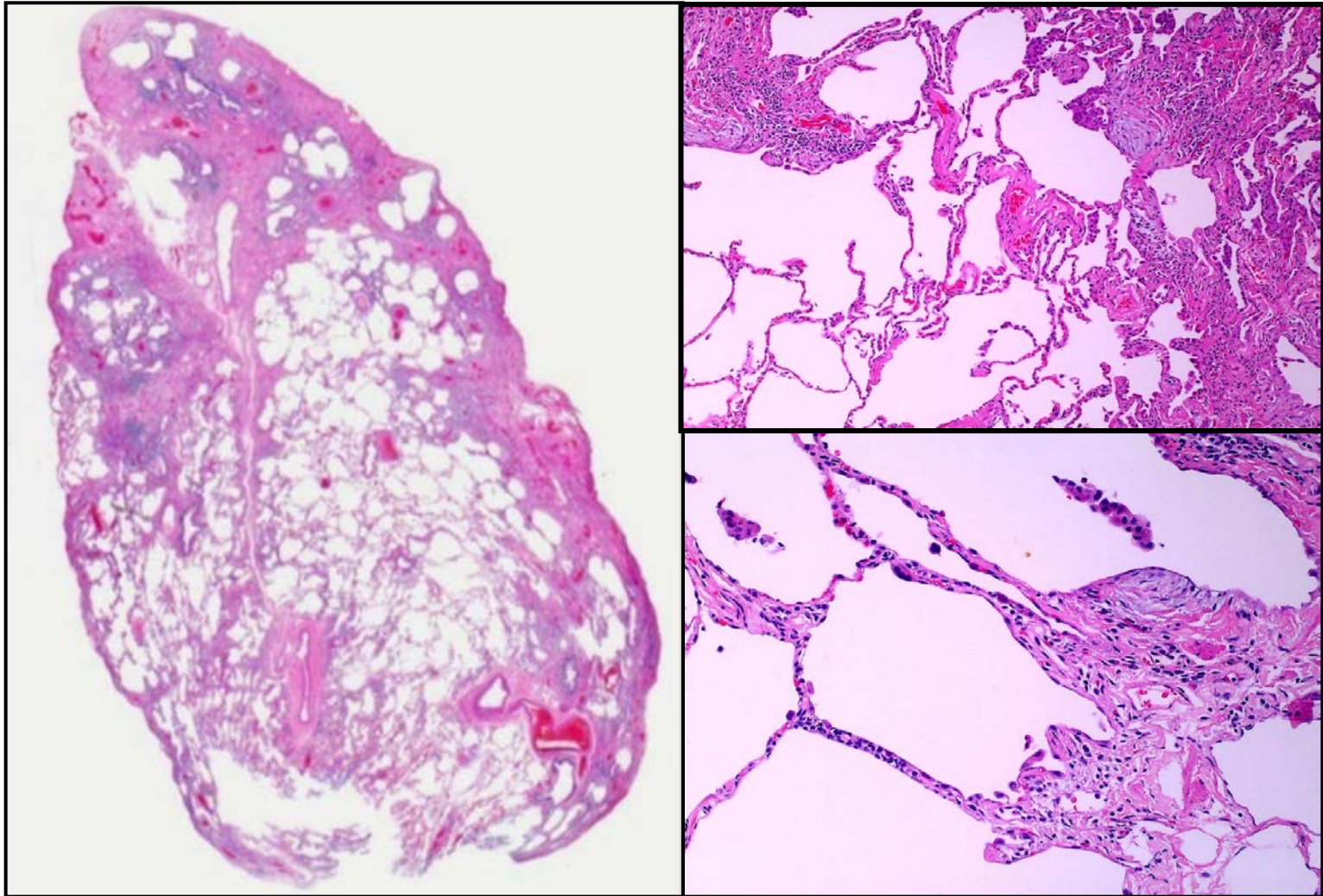
- 5 year survival rate (USA) is only 20-40%<sup>7</sup>
- Worse survival rates than many common cancers

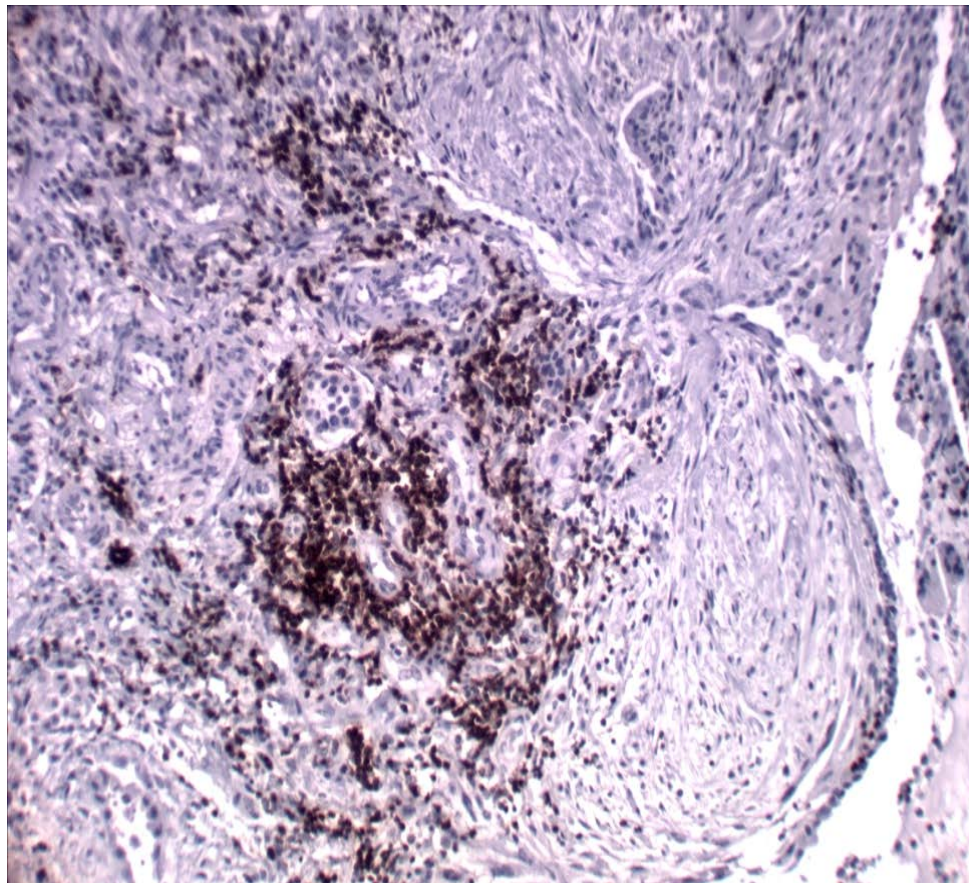


Reprinted with permission from Vancheri et al., Eur Respir J 2010<sup>7</sup>

This material has not been reviewed by European Respiratory Society prior to release; therefore the European Respiratory Society may not be responsible for any errors, omissions or inaccuracies, or for any consequences arising there from, in Eur Respir J March 2010 35:496-504; doi:10.1183/09031936.00077309

# Pathology: UIP Pattern





**T-cells in IPF Lungs.** Immunohistochemical staining shows that abnormal CD3<sup>+</sup> T-cell infiltrates (black cells near arrow) in lungs of IPF patients with usual interstitial pneumonia are distributed heterogeneously, and are often especially prominent in proximity to fibroproliferative foci (star).

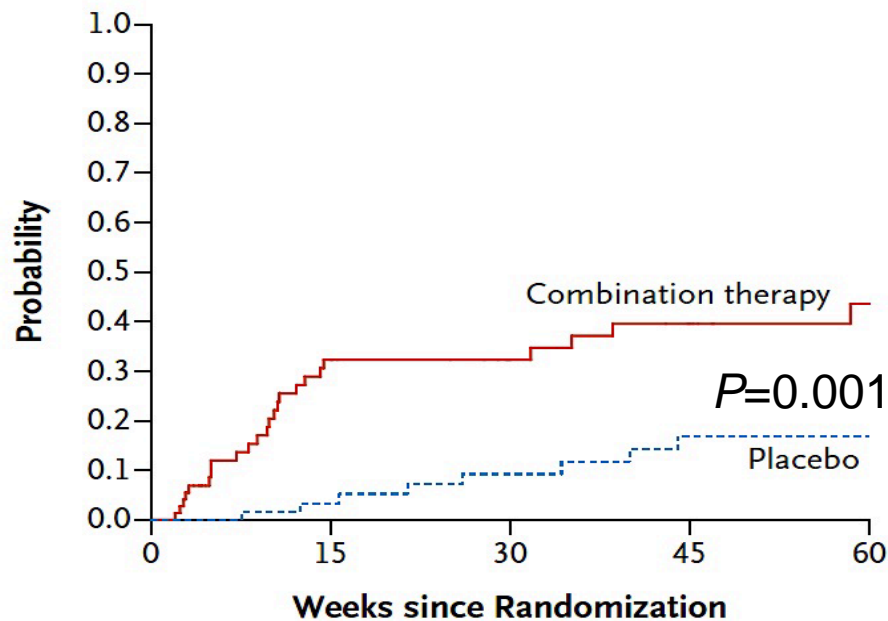
These infiltrates include both CD4<sup>+</sup> and CD8<sup>+</sup> T-cells (not shown). Similar associations between infiltrating T-cells and fibroproliferation are present in other chronic human diseases. *Image courtesy of G. Rosen. (10x).*



# Prednisone, Azathioprine, and N-Acetylcysteine for Pulmonary Fibrosis

The Idiopathic Pulmonary Fibrosis Clinical Research Network\*

## Time to Death or Hospitalization

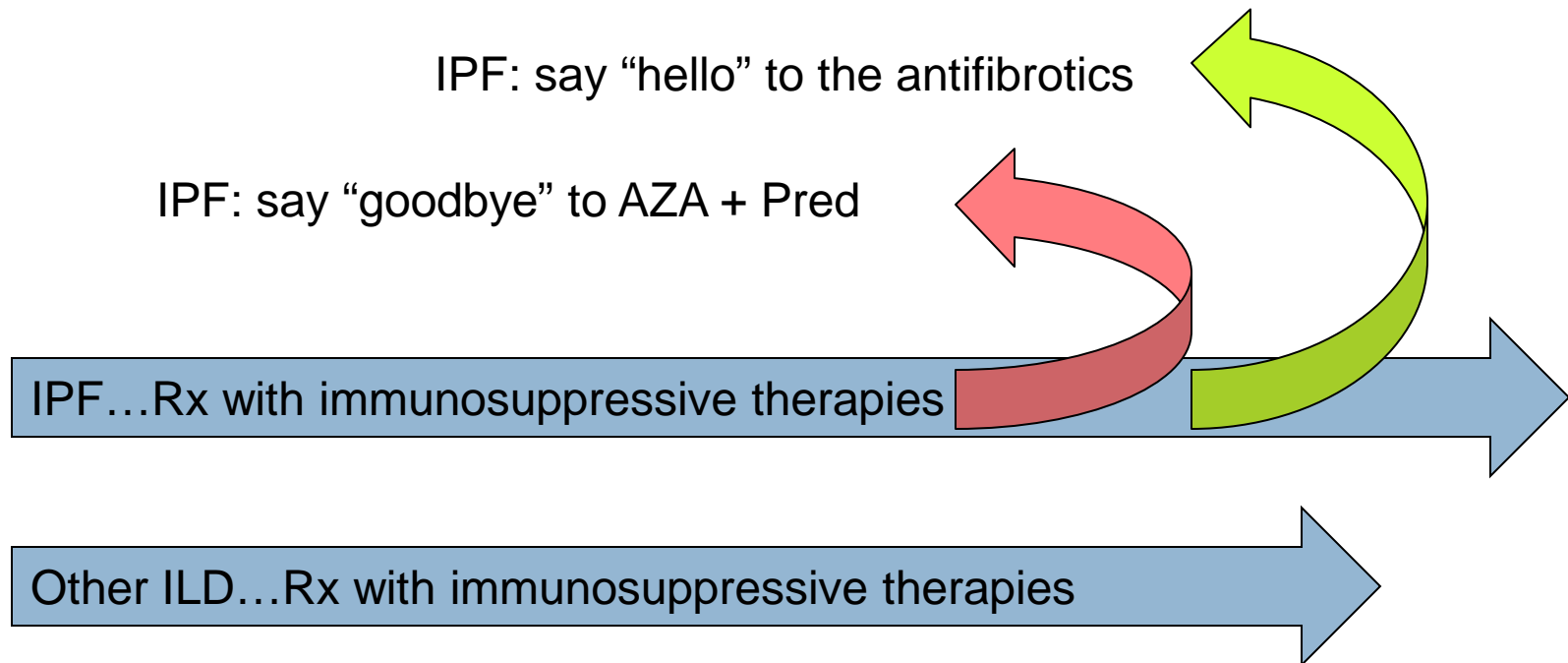


### No. at Risk

Combination therapy	77	40	29	23	10
Placebo	78	55	42	26	16

# SEISMIC TREATMENT PARADIGM SHIFT

IPF, IIPs and CTD-ILD= historic parallel treatment paths



ORIGINAL ARTICLE

# A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis

*The* NEW ENGLAND  
JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

MAY 29, 2014

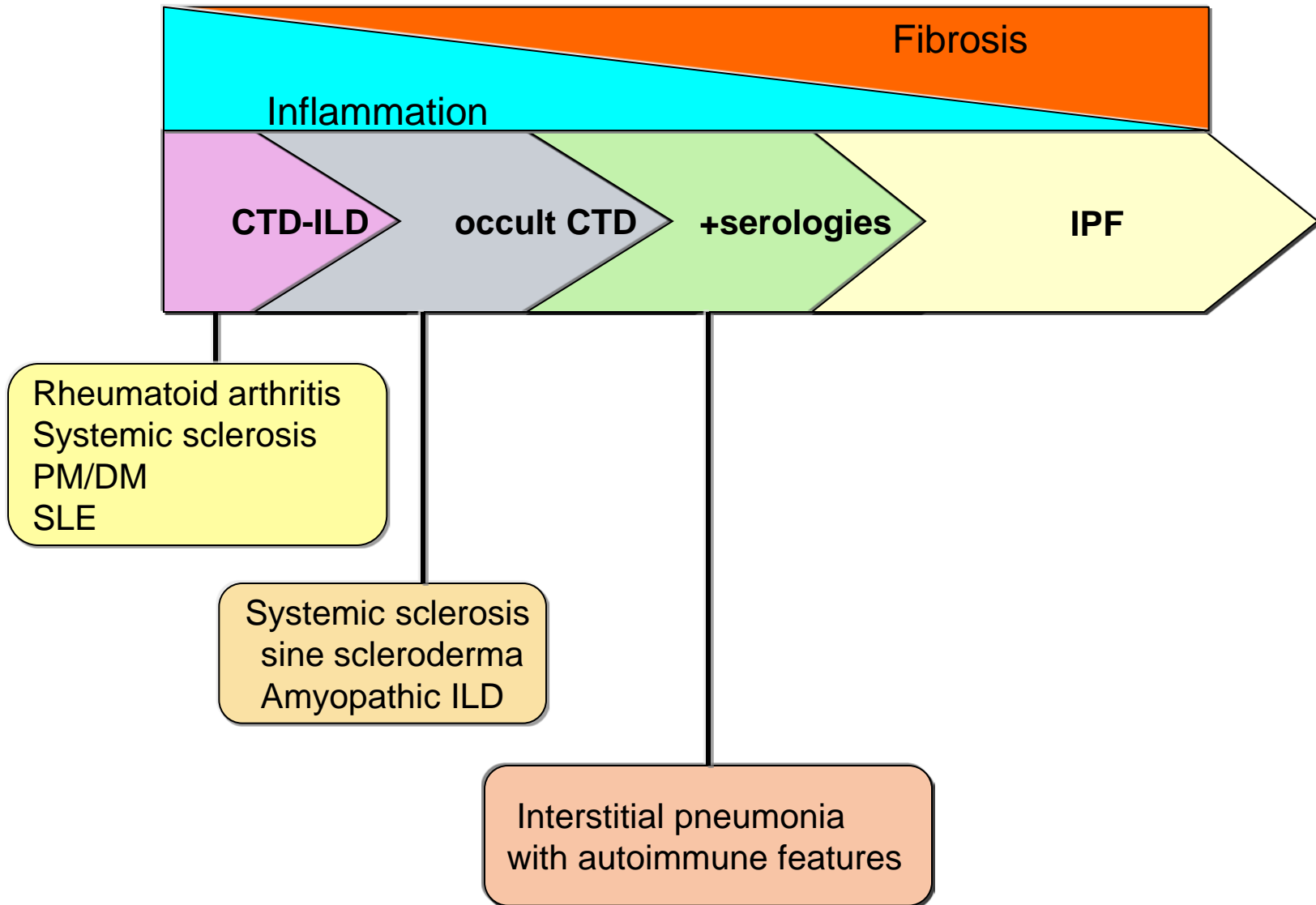
VOL. 370 NO. 22

## Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

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

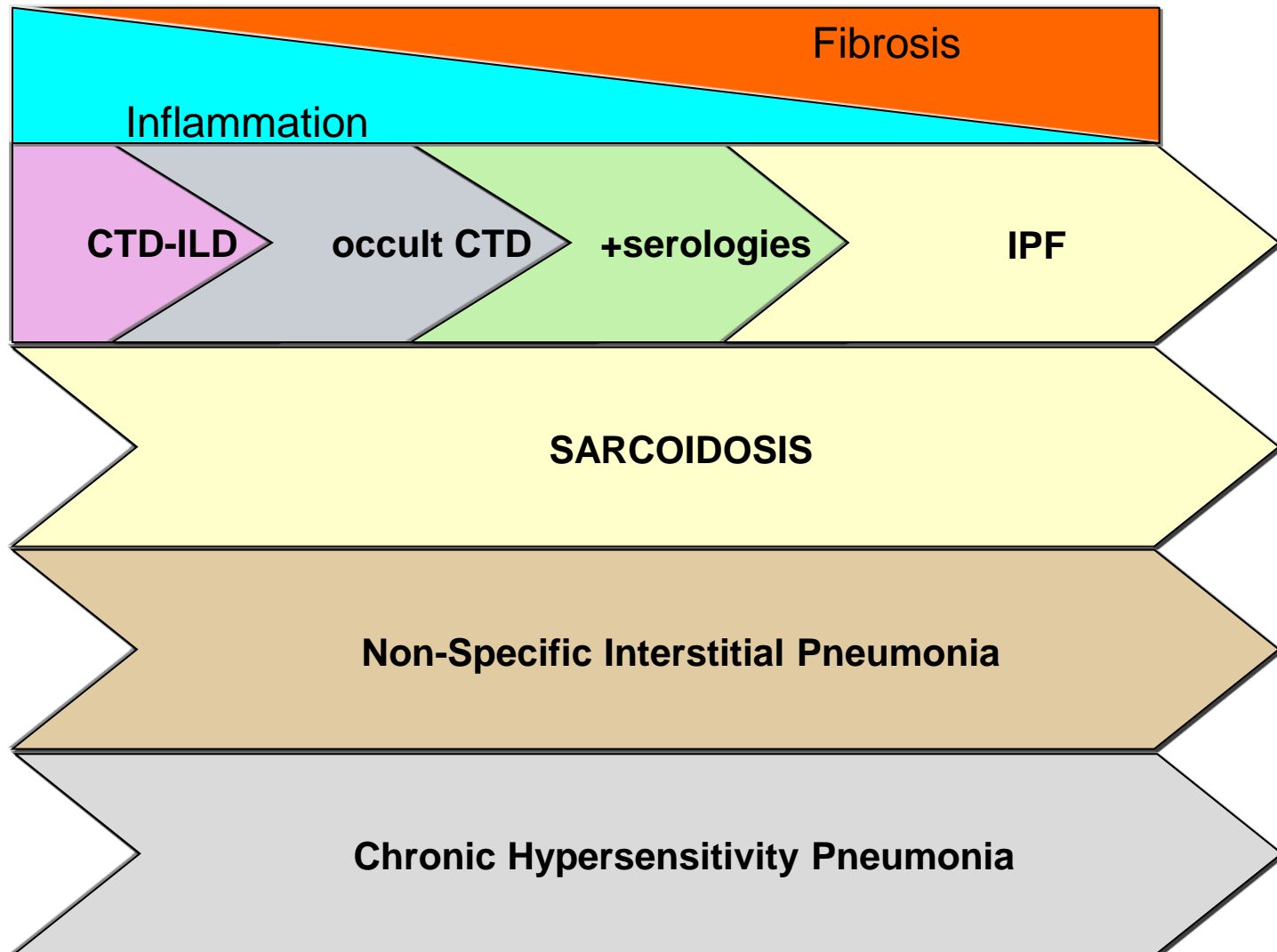
Richeldi L, et al. *N Engl J Med.* 2014;370:2071-2082.

# INTERSTITIAL LUNG DISEASE: A SPECTRUM

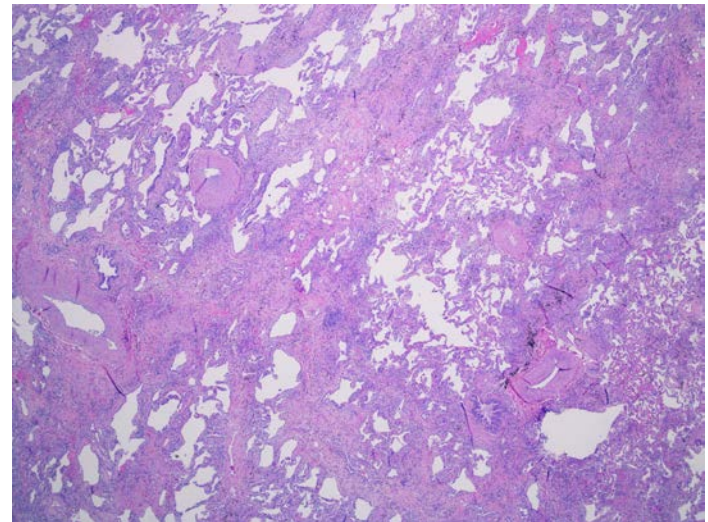
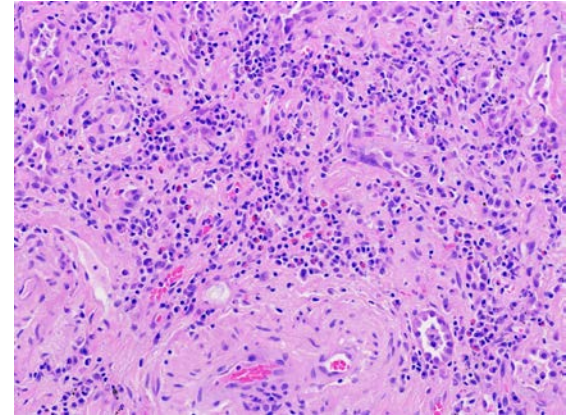


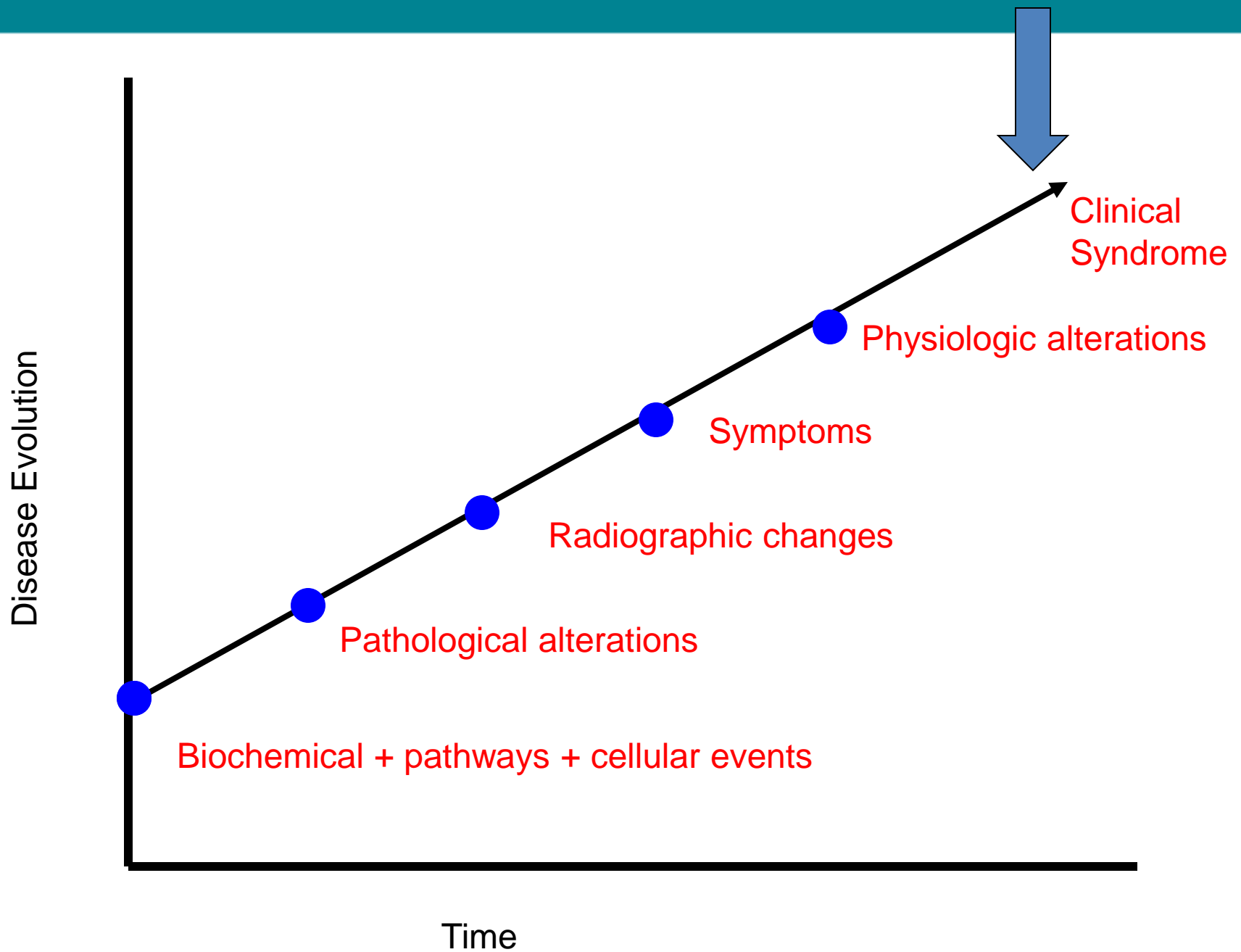


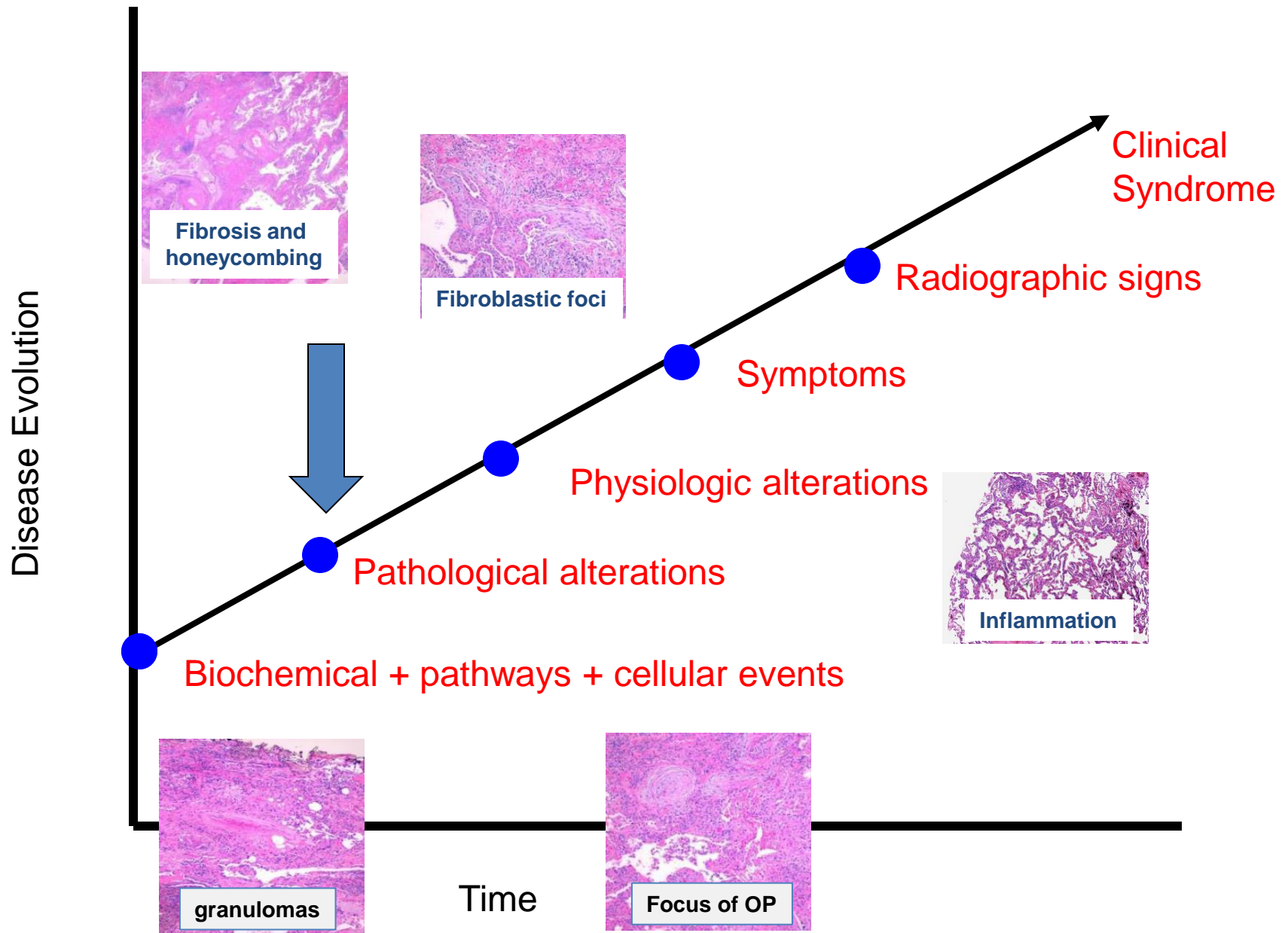
# INTERSTITIAL LUNG DISEASE: A SPECTRUM



# Same Case with Differing Pathology

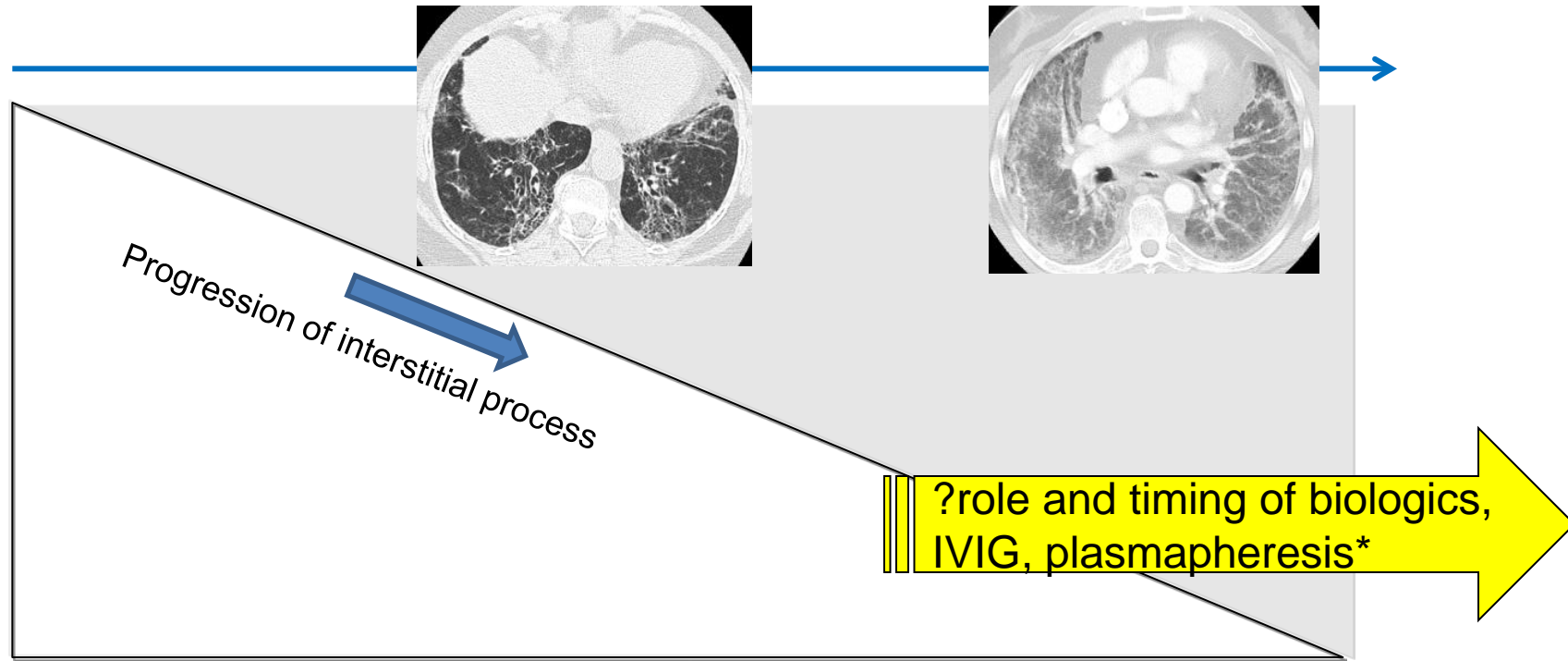




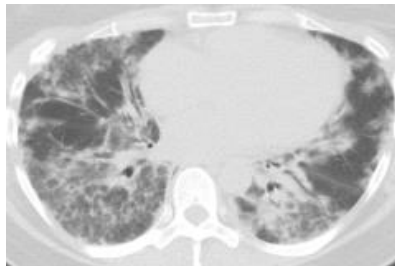


# CTD-ILD: conceptual framework for future therapeutic approach

Acute exacerbation



Therapy || ImmunoRx



|| ?antifibrotic\*

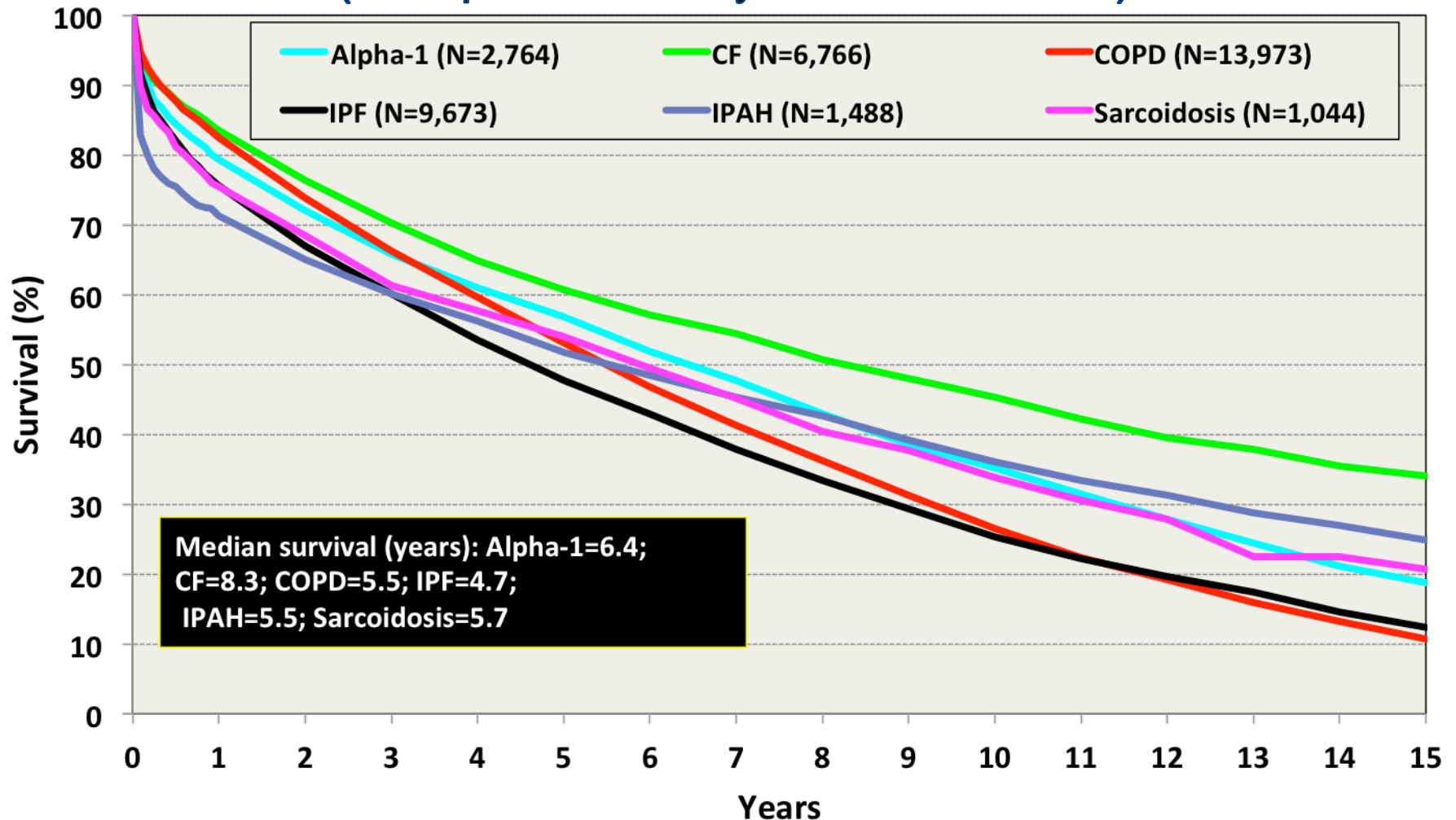
\*not recommended, await RCT evidence

|| ?PAH therapy \*

# Adult Lung Transplants

## Kaplan-Meier Survival by Diagnosis

(Transplants: January 1990 – June 2012)



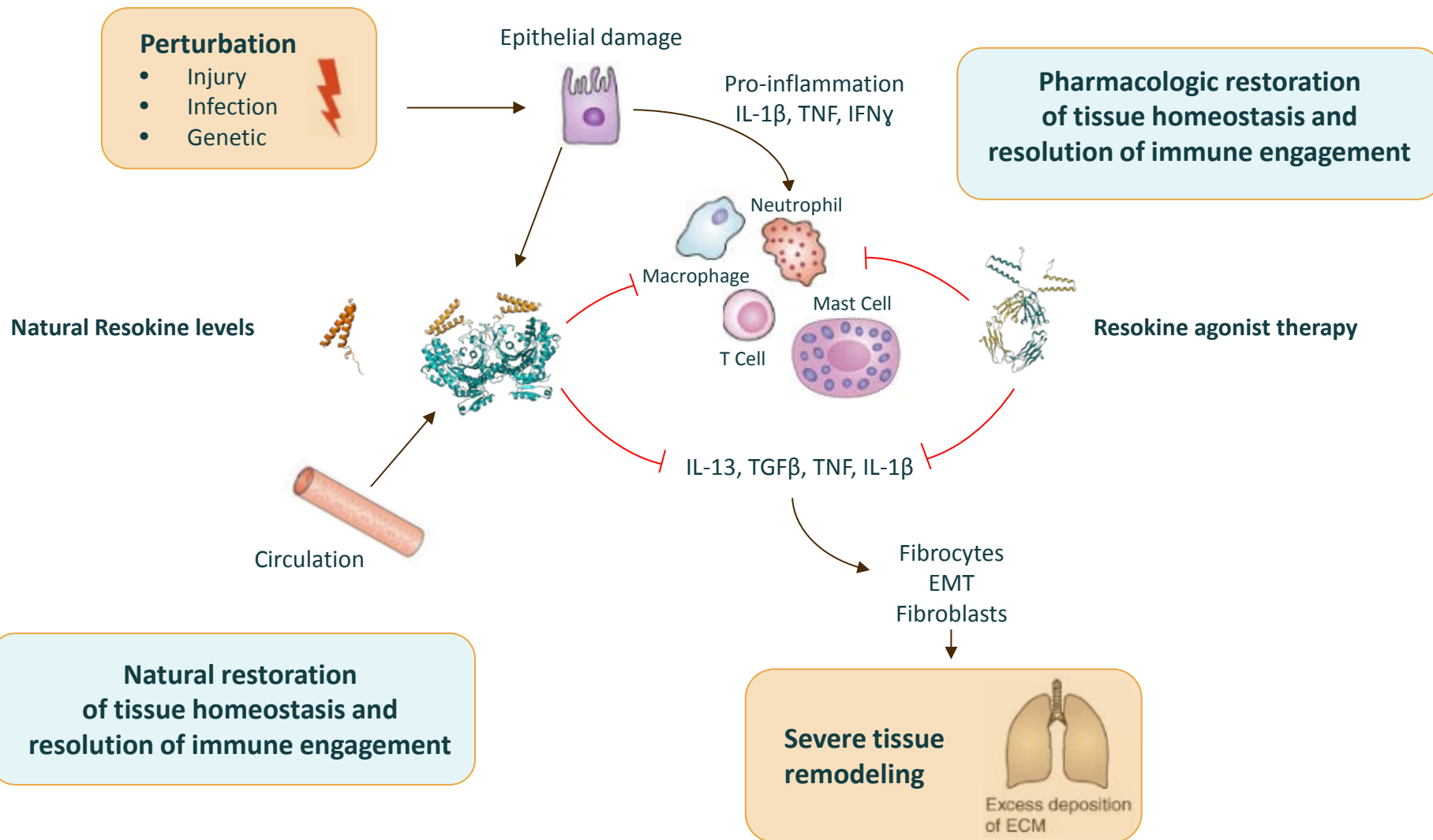




# iMod.Fc Program

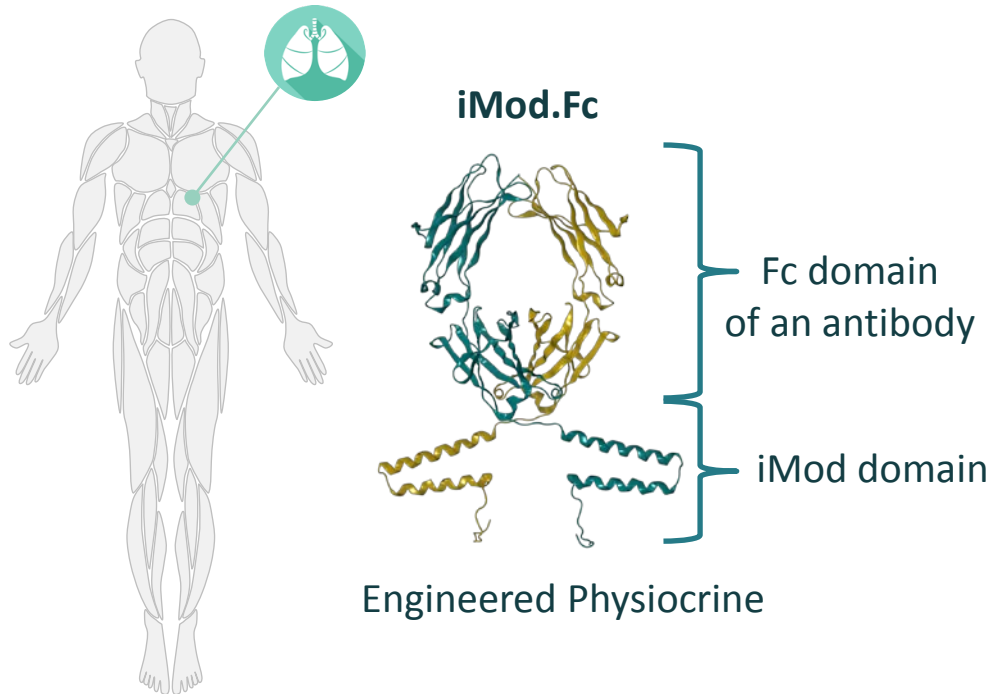
Lung Physiocrine Engineered to Treat Multiple Pulmonary Diseases

# Resokine Promotes Lung Homeostasis



# iMod.Fc Overview

*Opportunity for Lung Patients*



**iMod domain:** Resokine splice variant relatively more expressed in **lung** than other tissues

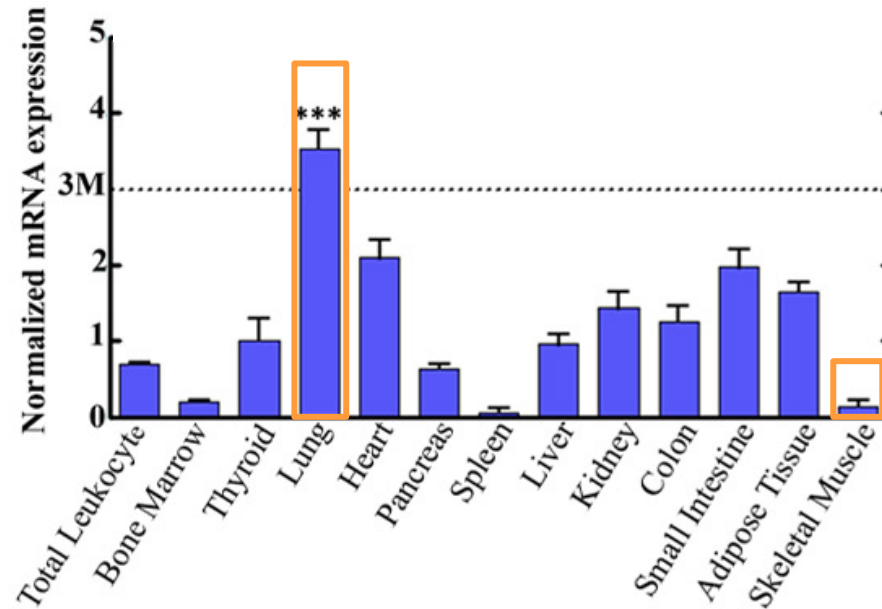
**Fc domain:** increased exposure to potentially enable **once-monthly dosing in humans**

**Engineered result:** iMod.Fc ~350x increased exposure vs. iMod; while retaining T cell modulation activity

**1<sup>st</sup> molecule** from internal Fc platform

# iMod Domain in Lung

*Splice Variant Express Data for iMod in Lung*

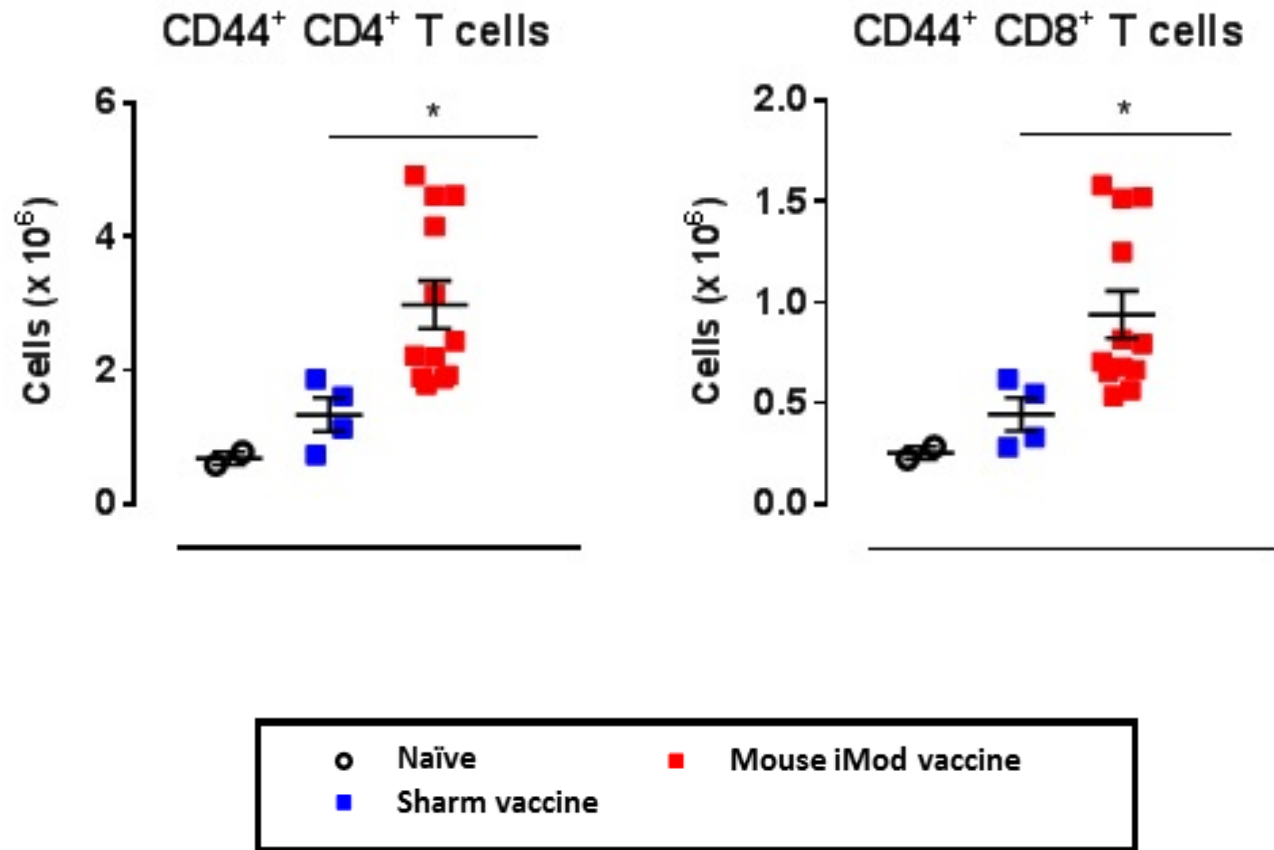


**Splice variant** for the **iMod domain** is relatively more expressed in **lung** than other tissues

# Functional Knockout of Resokine Pathway Increases T Cell Invasion Post Disease Induction

*Rodent functional knockout inducing idiopathic pulmonary disease using Bleomycin*

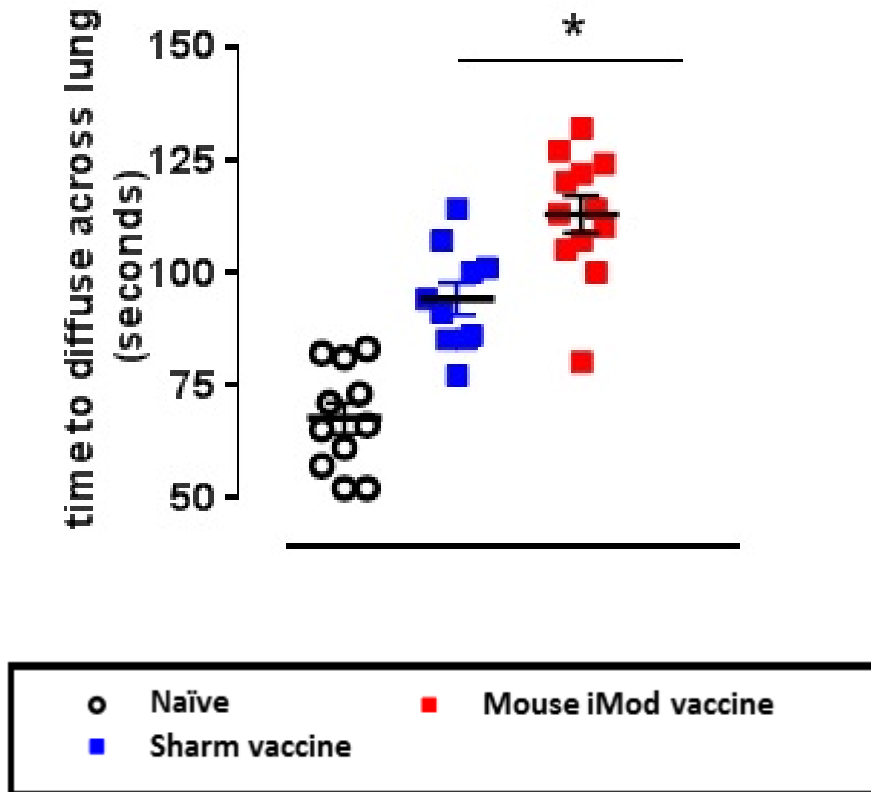
## T cell Invasion



# Functional Knockout of Resokine Pathway Increases T Cell Invasion Post Disease Induction

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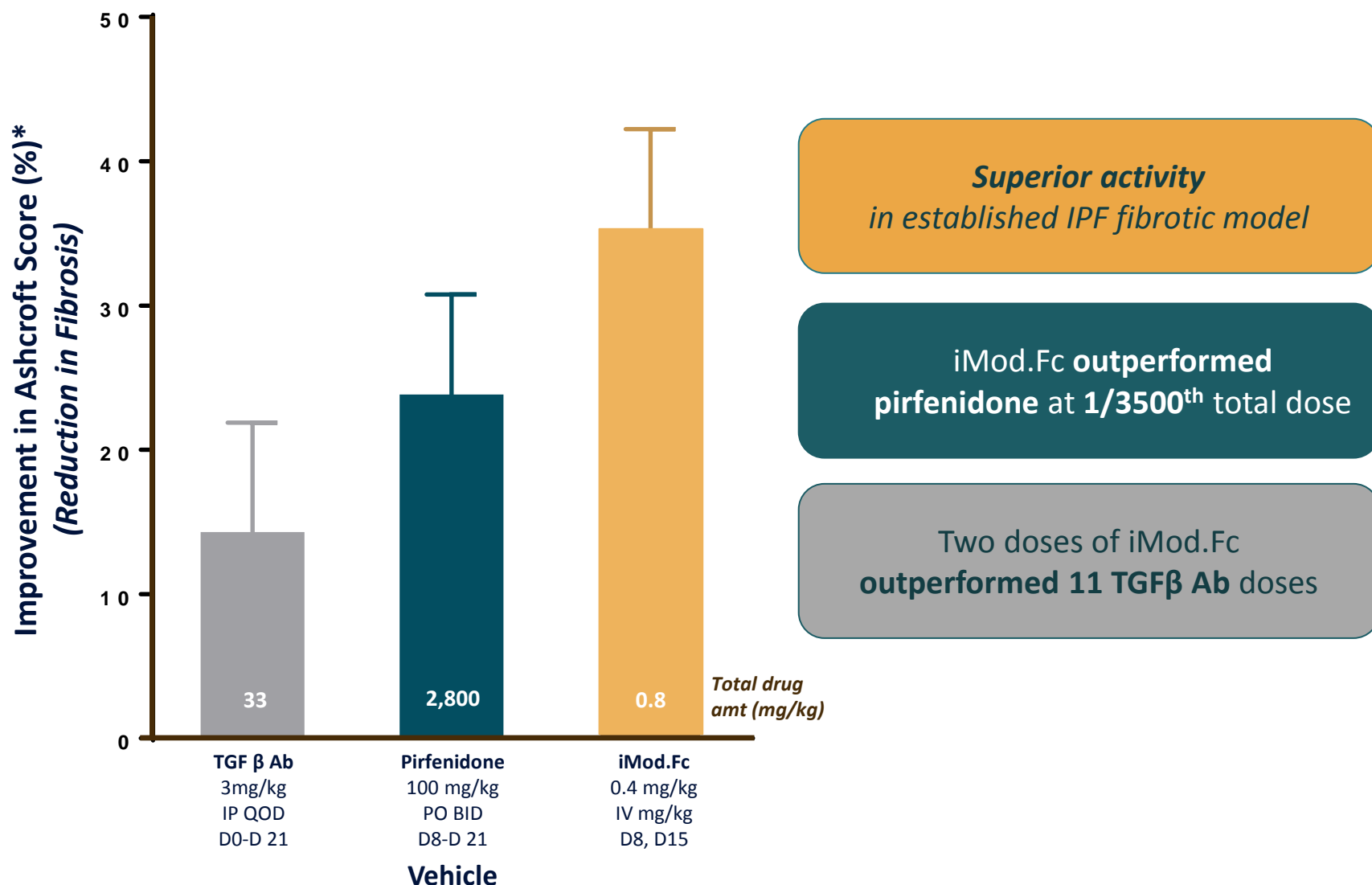
## Impairment of lung function





# iMod.Fc (Resokine Pathway) Outperforms Current Treatments

*Established Rodent Model for Idiopathic Pulmonary Fibrosis (IPF)*



# iMod.Fc: Status and 2017 Development Goals

## Milestones:

- ✓ Activity in industry proven model of IPF (approved drugs Pirfenidone & Nintedanib)
- ✓ GMP manufacturing kicked off
- ✓ Rat/non-human primate non-GLP safety & PK data support advancement to IND

## 2017 Development Goals:

**Biomarker/MOA:** Introduce mechanistic/PD assay

**IND Enabling:** Initiate preclinical safety studies

**GMP Manufacturing:** Complete initial clinical trial supply

**Clinical Trial:** Initiate first in human clinical trial



QUESTIONS?