



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

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

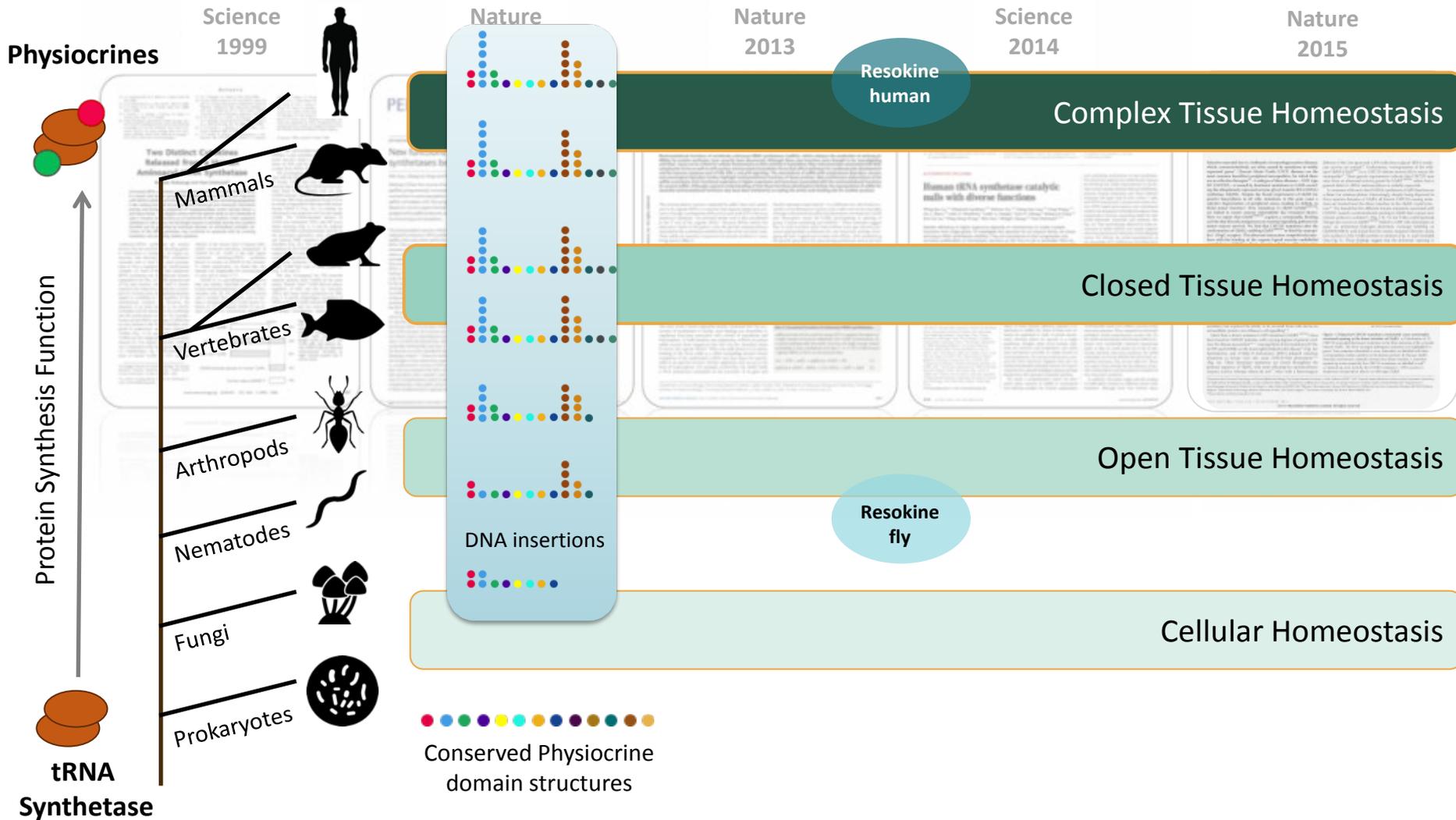


New Immunological Pathway: Resokine

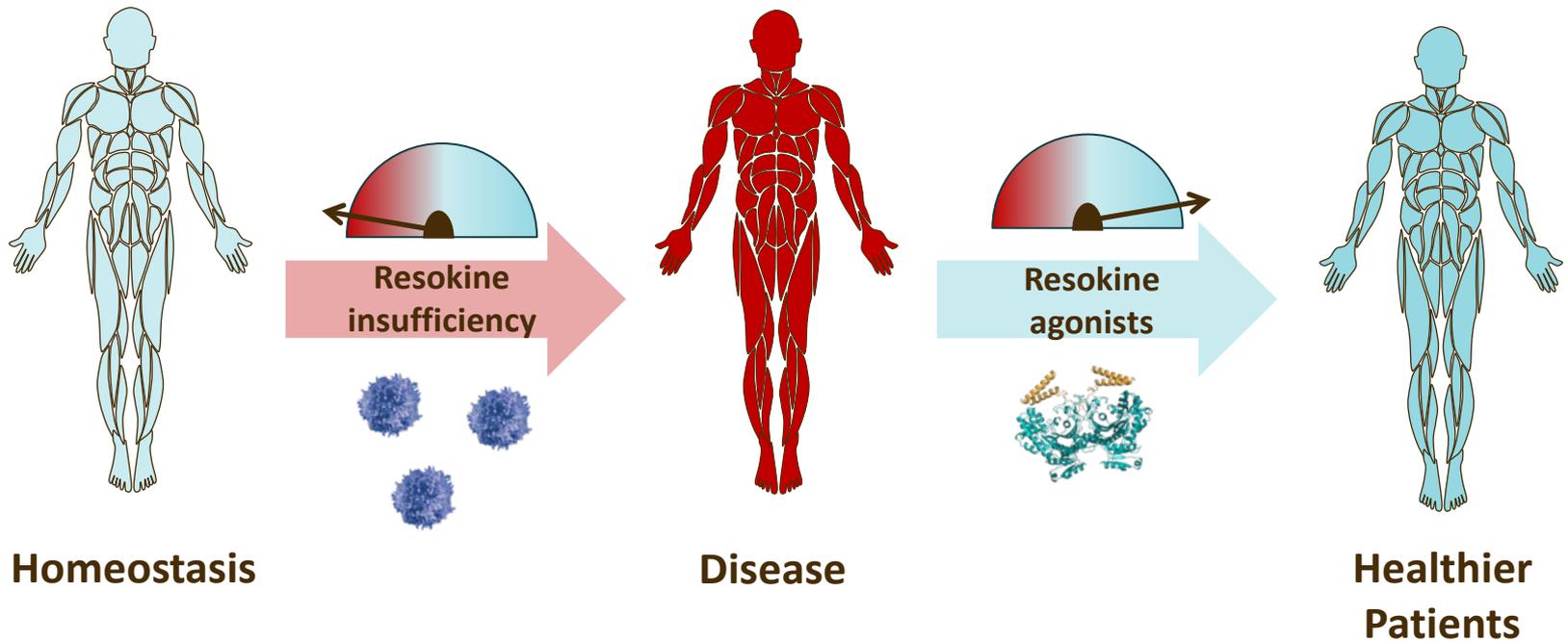
Evolved from Cellular Homeostasis Genes over 400 Million Years

Resokine: Potential Key Regulator of Homeostasis

Evolved with System Complexity



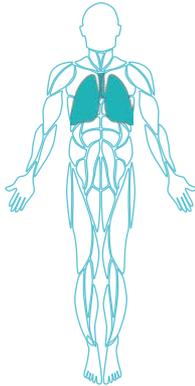
LIFE's Therapeutic Paradigm



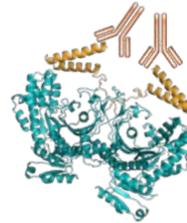
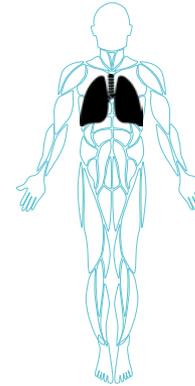
Disrupting the Resokine Pathway Promotes ILD

Evidence for Homeostatic Role of Resokine in Humans

Homeostasis



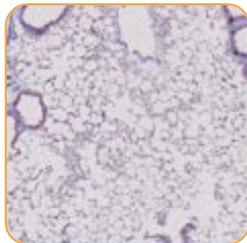
Imbalance



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

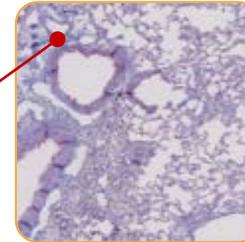


Disease antibodies



Healthy lung

↑ Immune cell
Invasion / activity

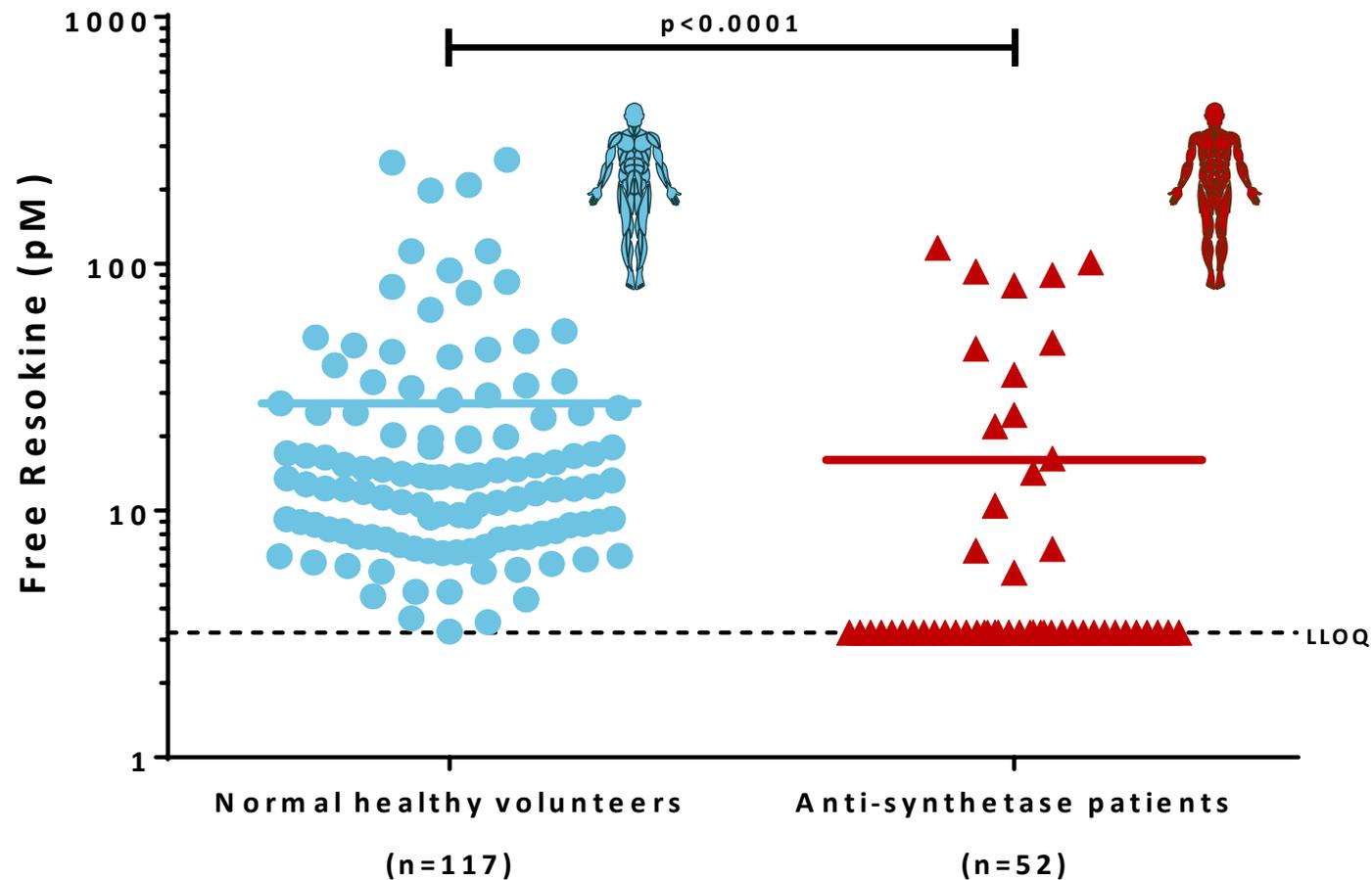


Diseased Lung

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

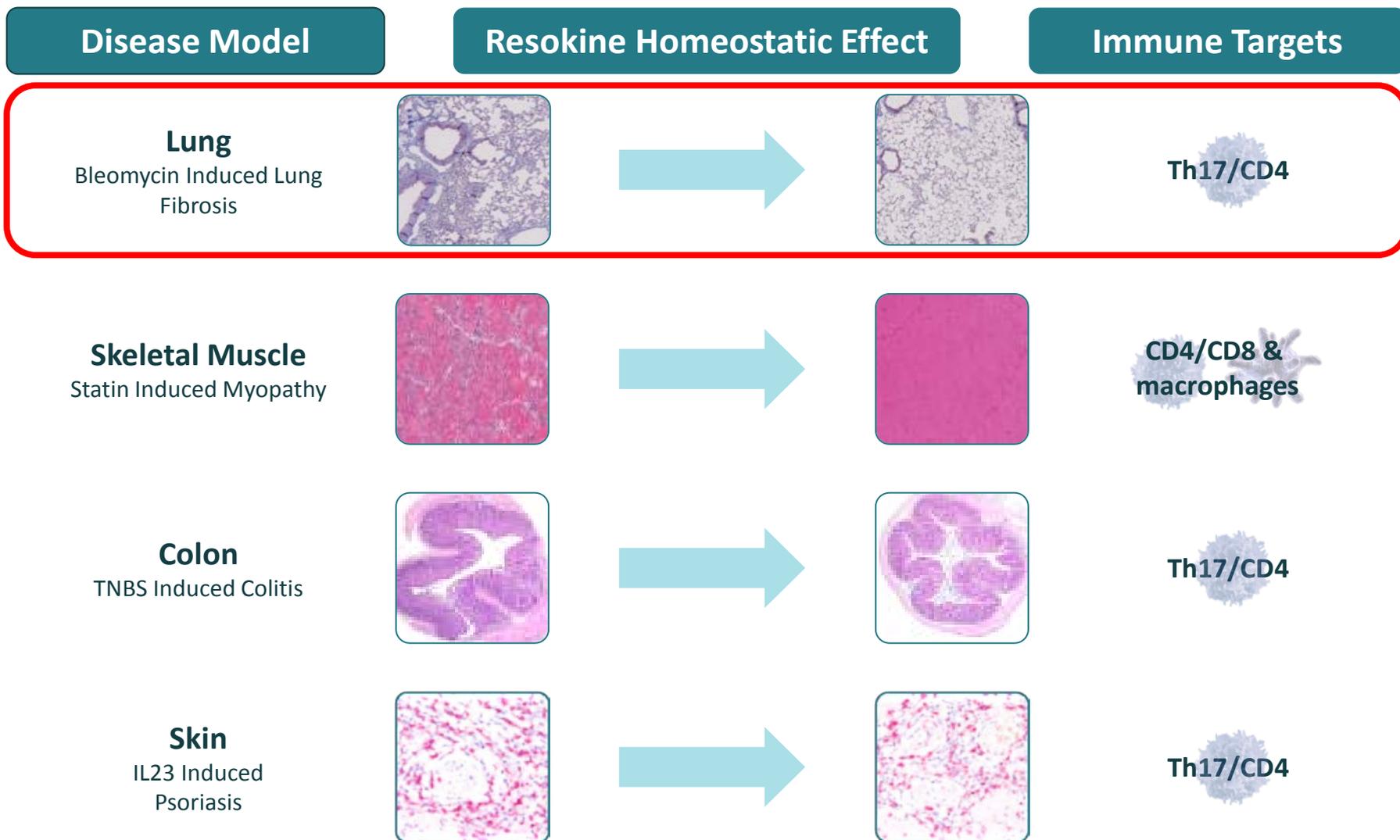


>85% of patients develop Interstitial Lung Disease (ILD)

69% at or below limit of detection

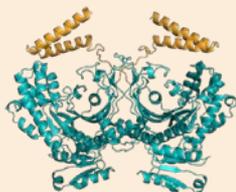
Agonists of the Resokine Pathway in Immune Driven Models

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



3rd 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

Steven Nathan, MD

Medical Director,

Advanced Lung Disease & Transplant Program

Inova Fairfax Hospital

Falls Church, Virginia USA

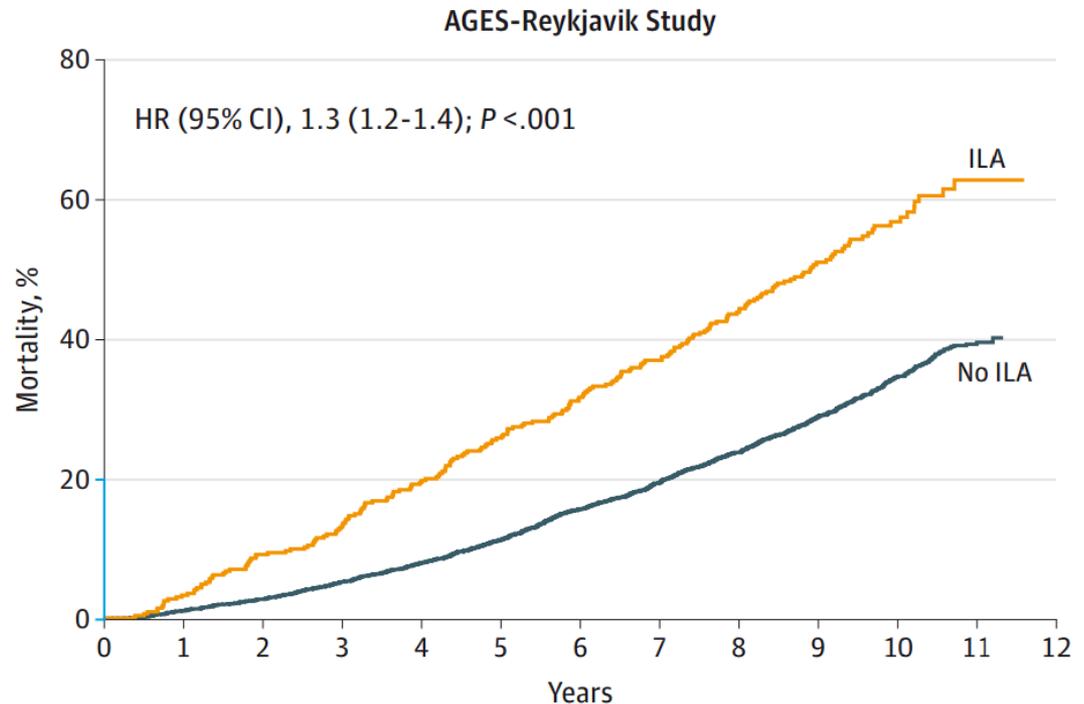
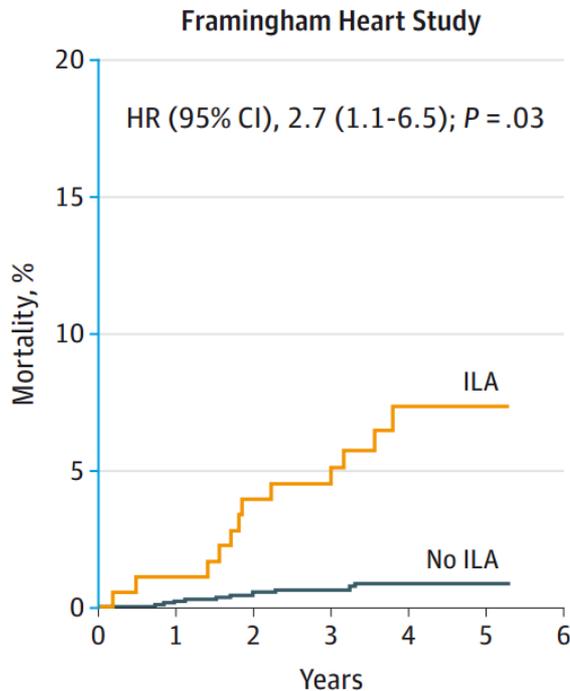


Disclosures: Steven Nathan, MD

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

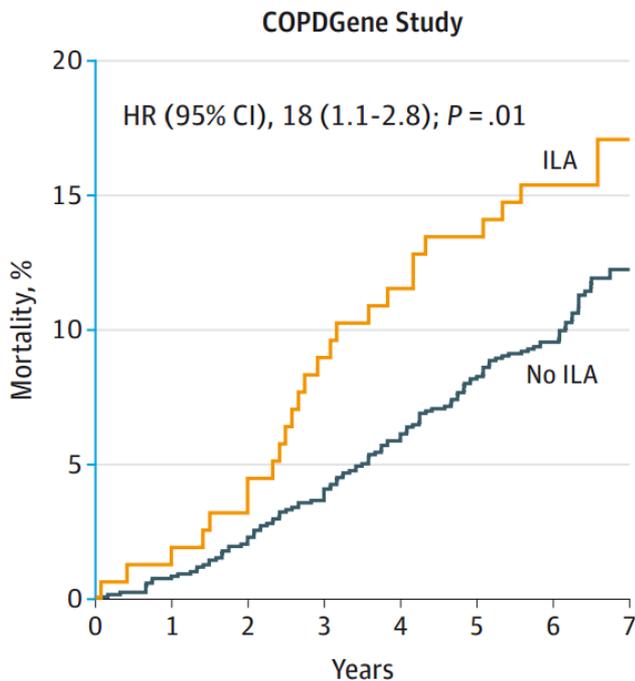
ILA	177	176	171	170	107
No ILA	1370	1367	1364	1361	1022

No. at risk

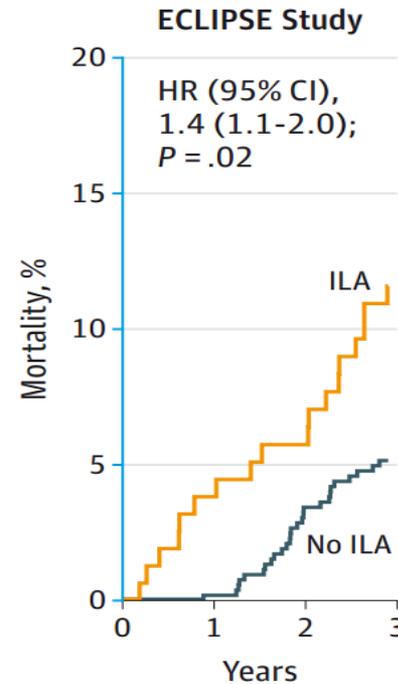
ILA	378	365	343	328	304	281	259	239	213	137	68	12
No ILA	3216	3177	3124	3044	2956	2851	2710	2589	2447	1694	862	228

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.

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



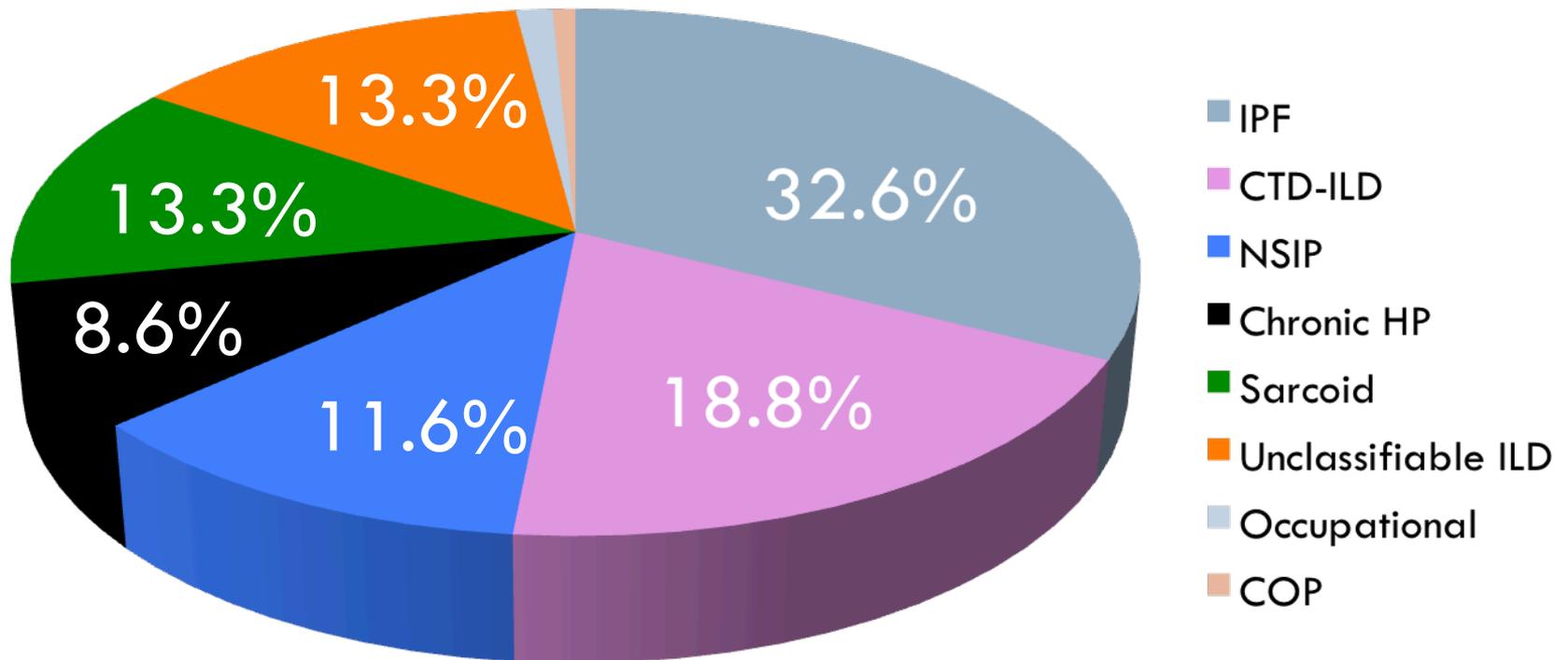
No. at risk				
ILA	156	151	145	
No ILA	528	525	505	

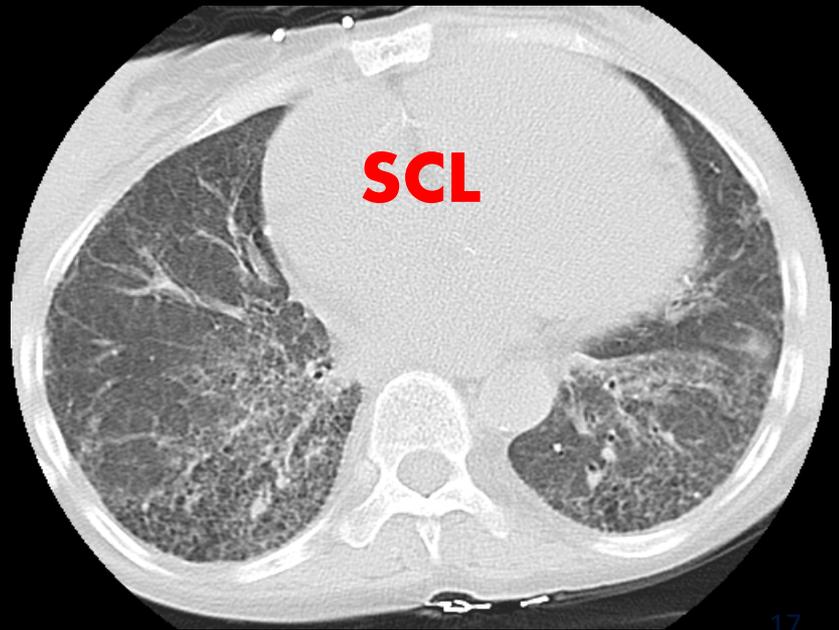
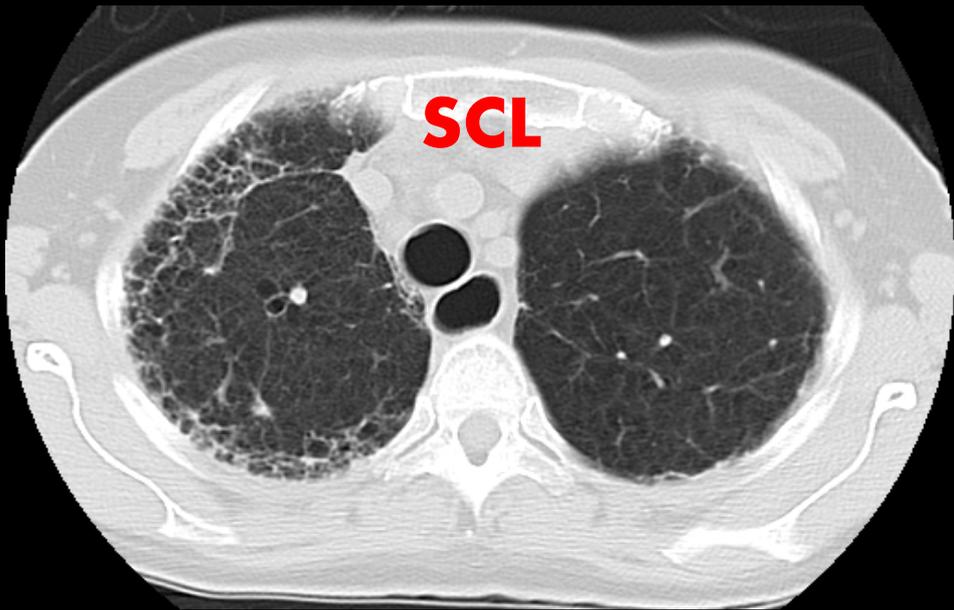
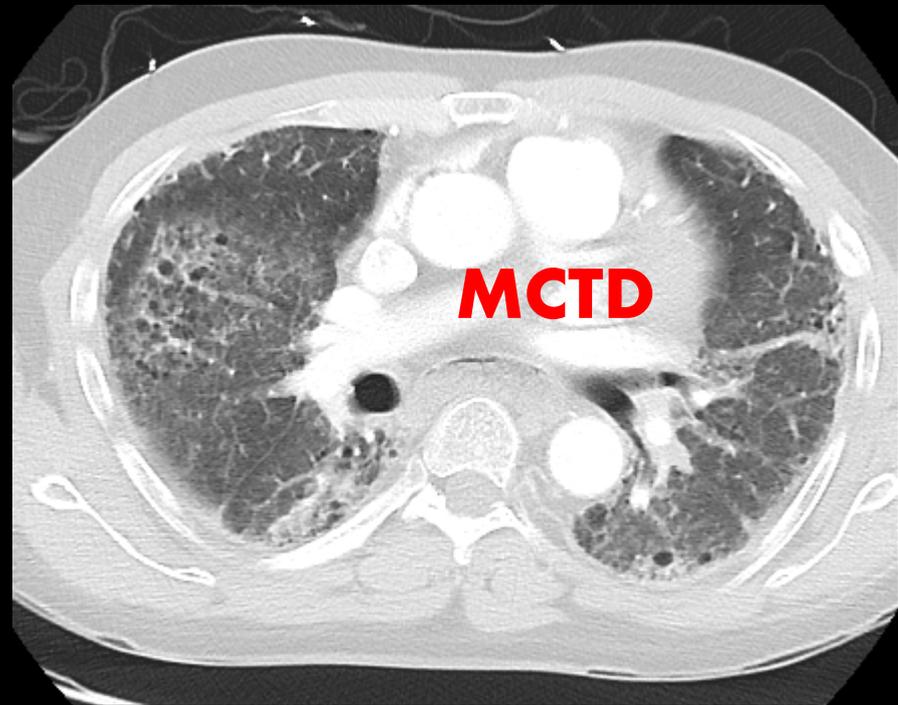
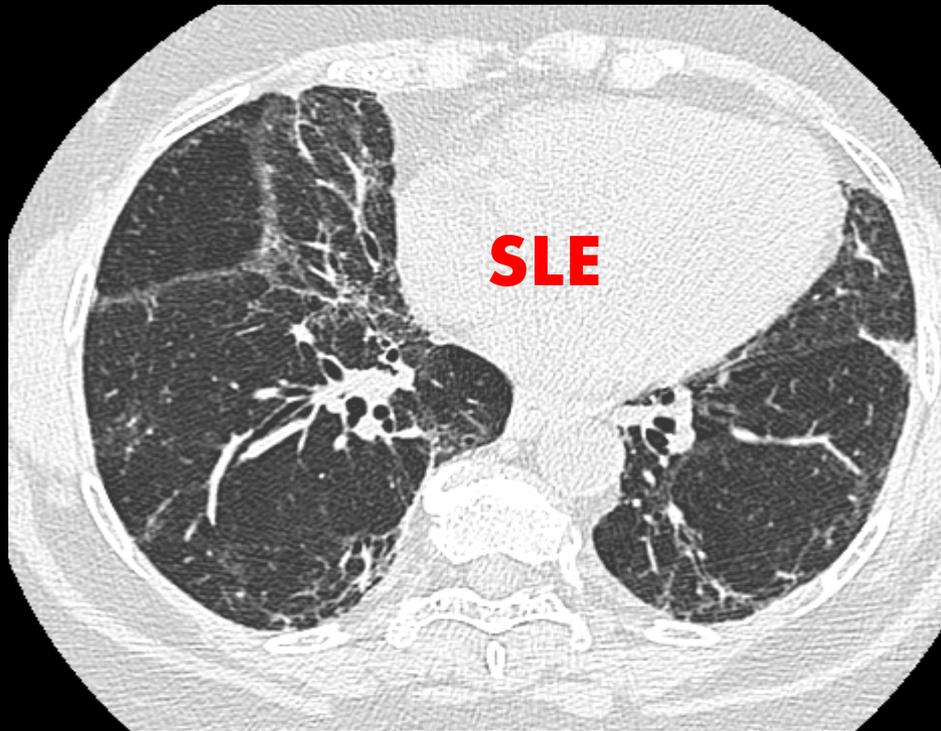
Blue segments of y-axes indicate mortality range from 0% to 20%. P values included in each panel are associated with hazard ratios (HRs [95% CIs]) from the adjusted Cox proportional hazards model including adjustments for age, sex, race, body mass index, pack-years of smoking, current or former smoking 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 Amyloidosis Lymphangiolyomyomatosis PLCH, Eosinophilic pneumonia. Neurofibromatosis, DAH	Unclassifiable	+++	+++
		COP	++	+
		RB-ILD	++	-
		DIP	++	+
		AIP	+/-	+
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)

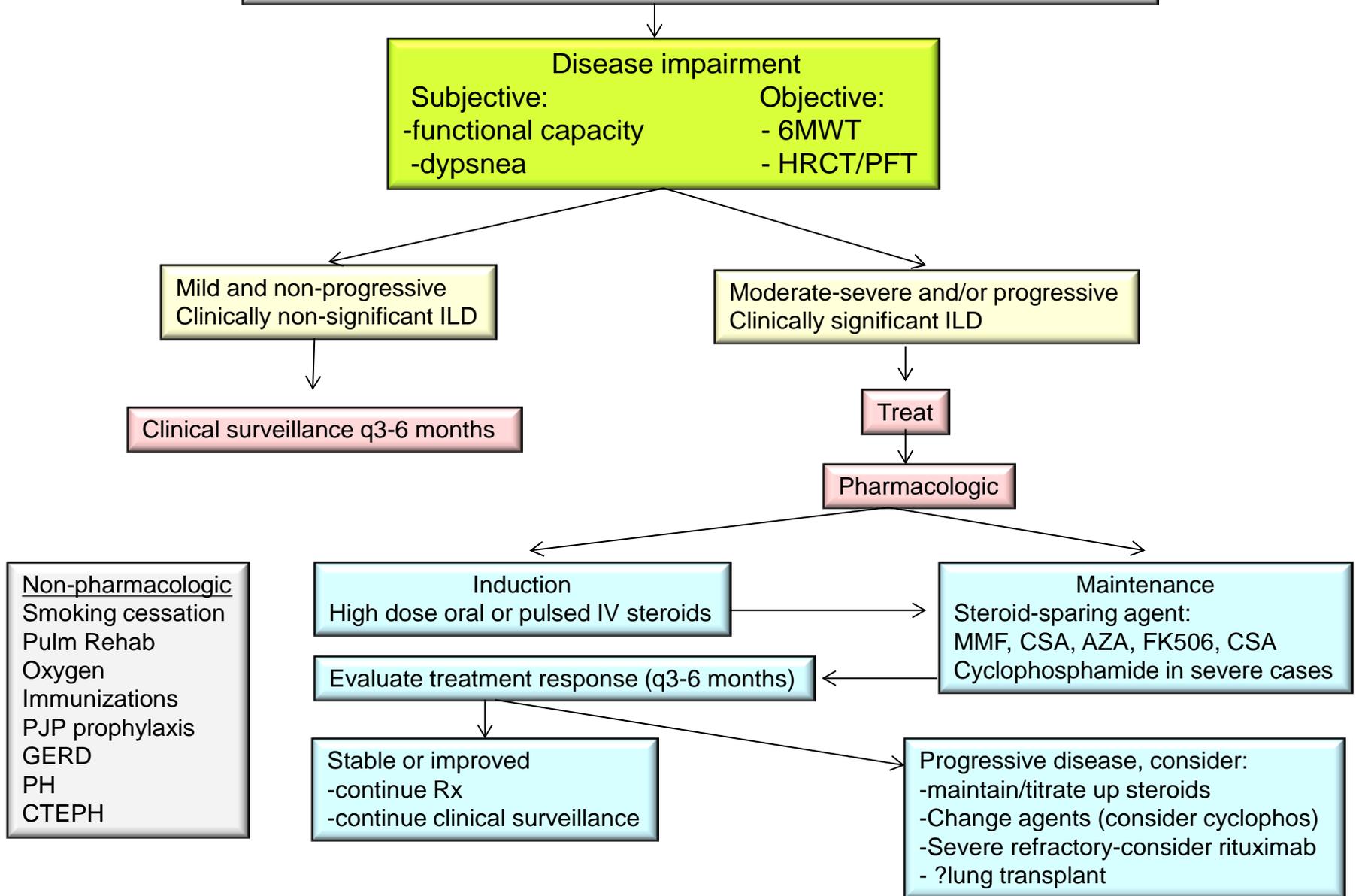




Prevalence of ILD in CTD

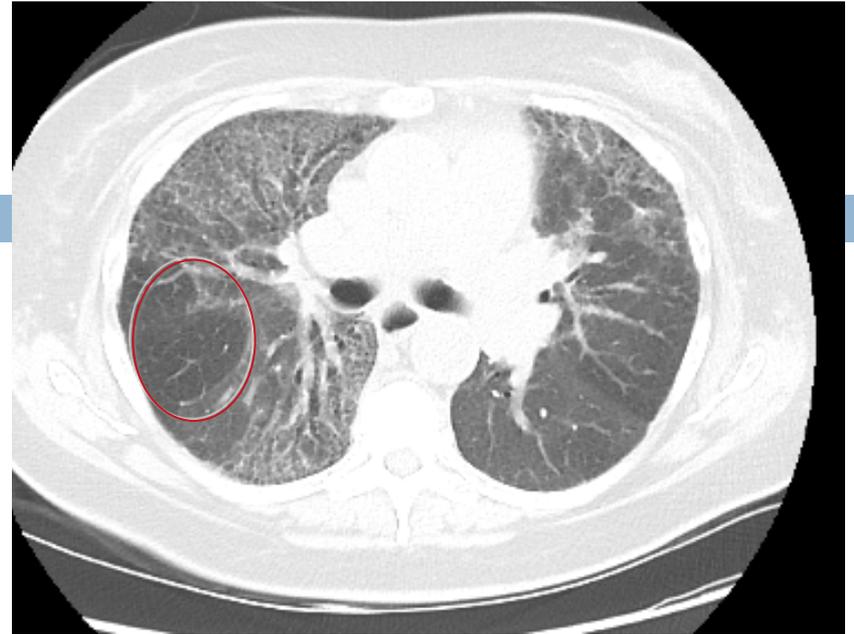
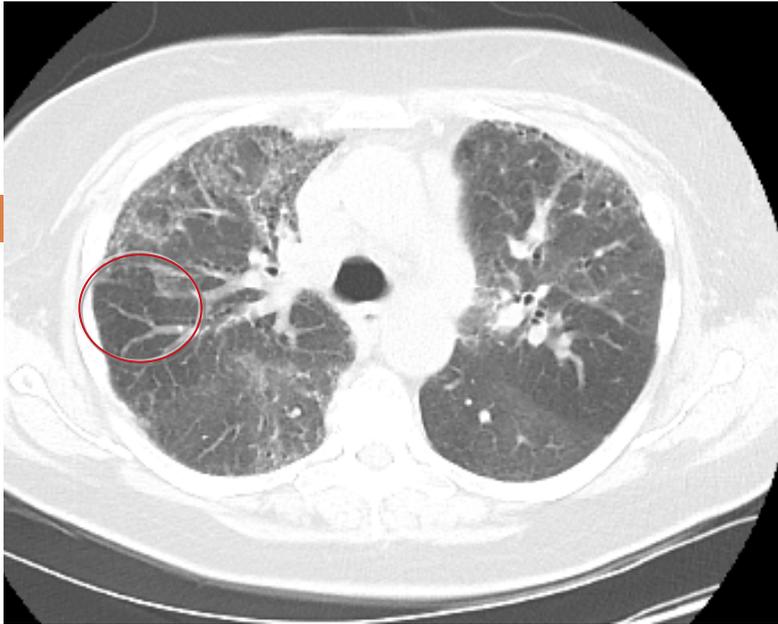
- 1,600 deaths in USA annually
 - ▣ 25% of all ILD deaths
 - ▣ 2% of respiratory deaths
- RA: 15-20%
- PM/DM: 5-20%
- SLE: 5-18%
- Scleroderma: 50-70%
- Sjogrens:5-40%

APPROACH TO THE TREATMENT OF CTD-ILD

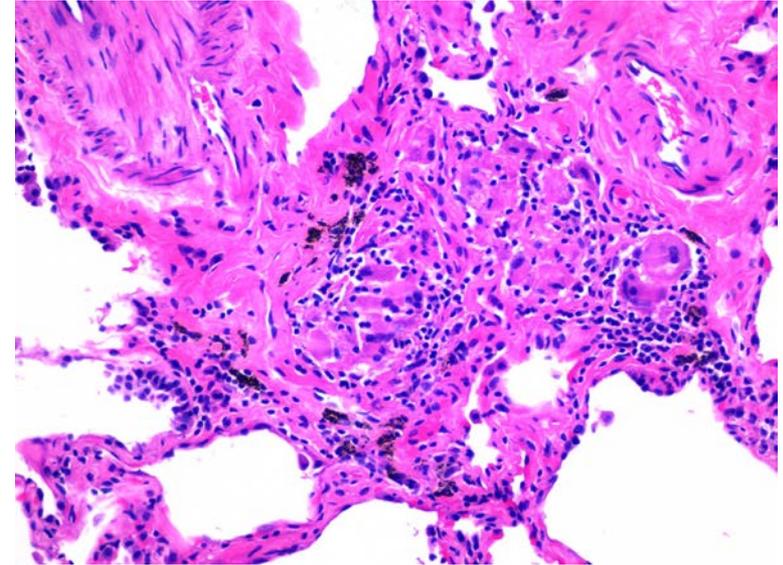
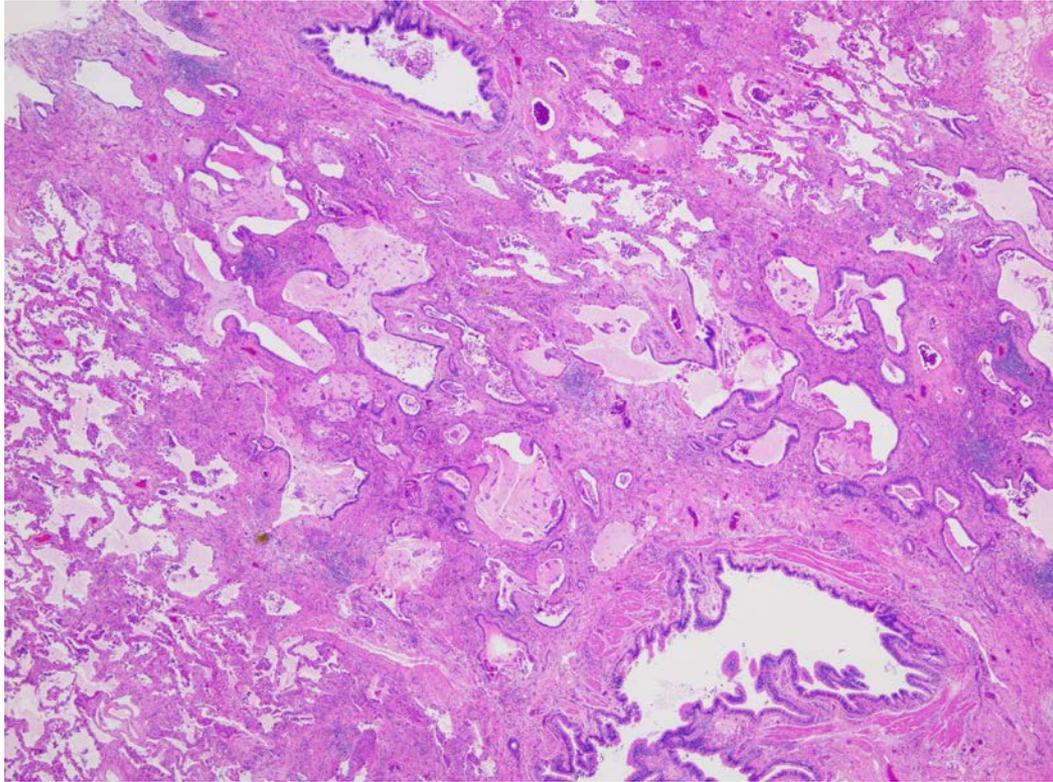


Chronic Hypersensitivity Pneumonitis

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



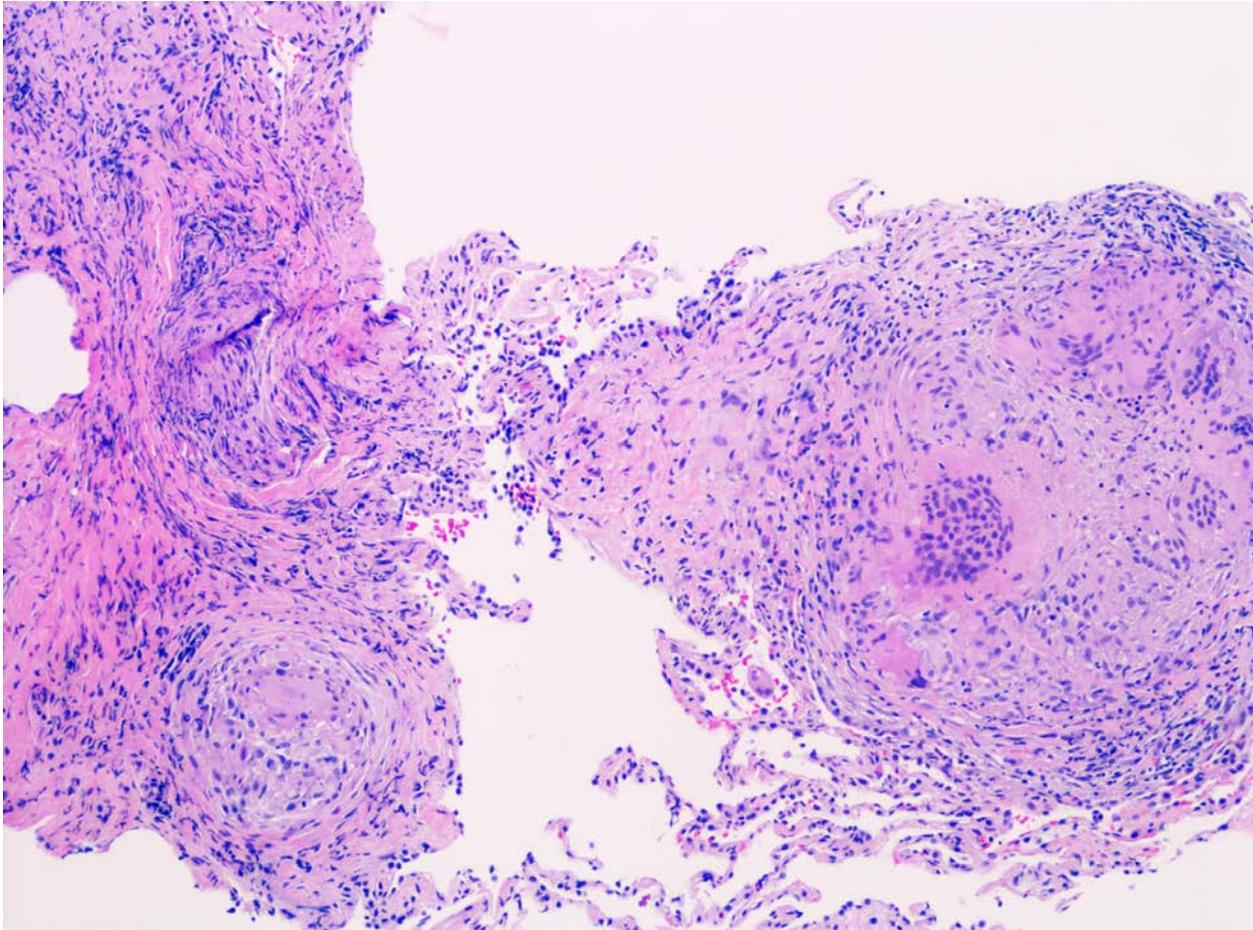
Chronic HP: Pathology

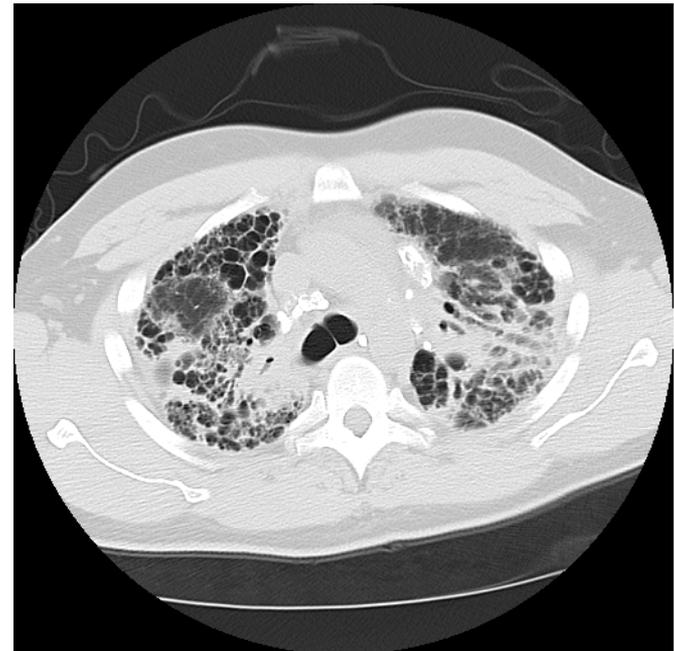
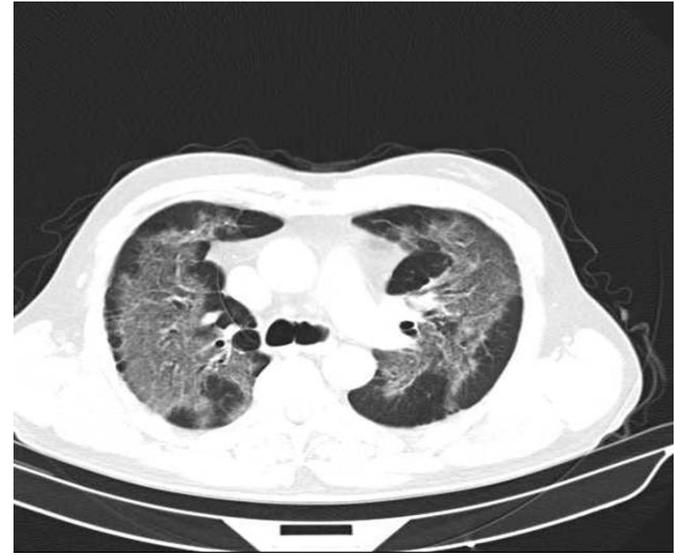
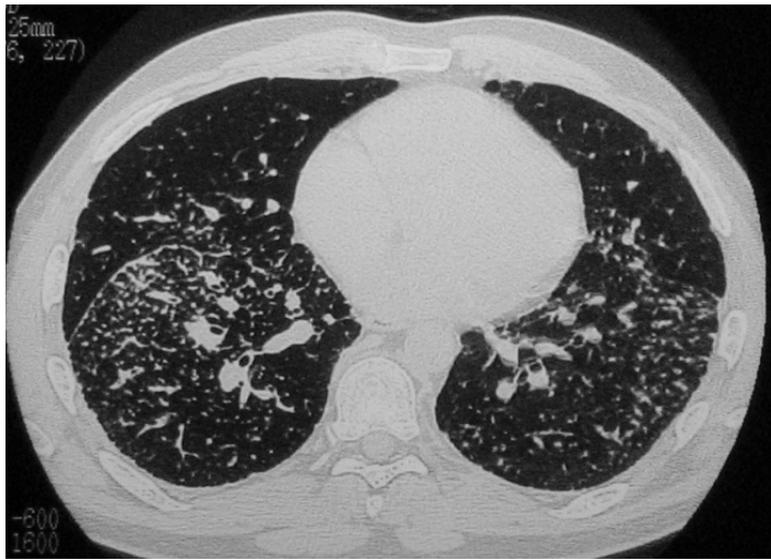


Sarcoidosis: Systemic Disease

- 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





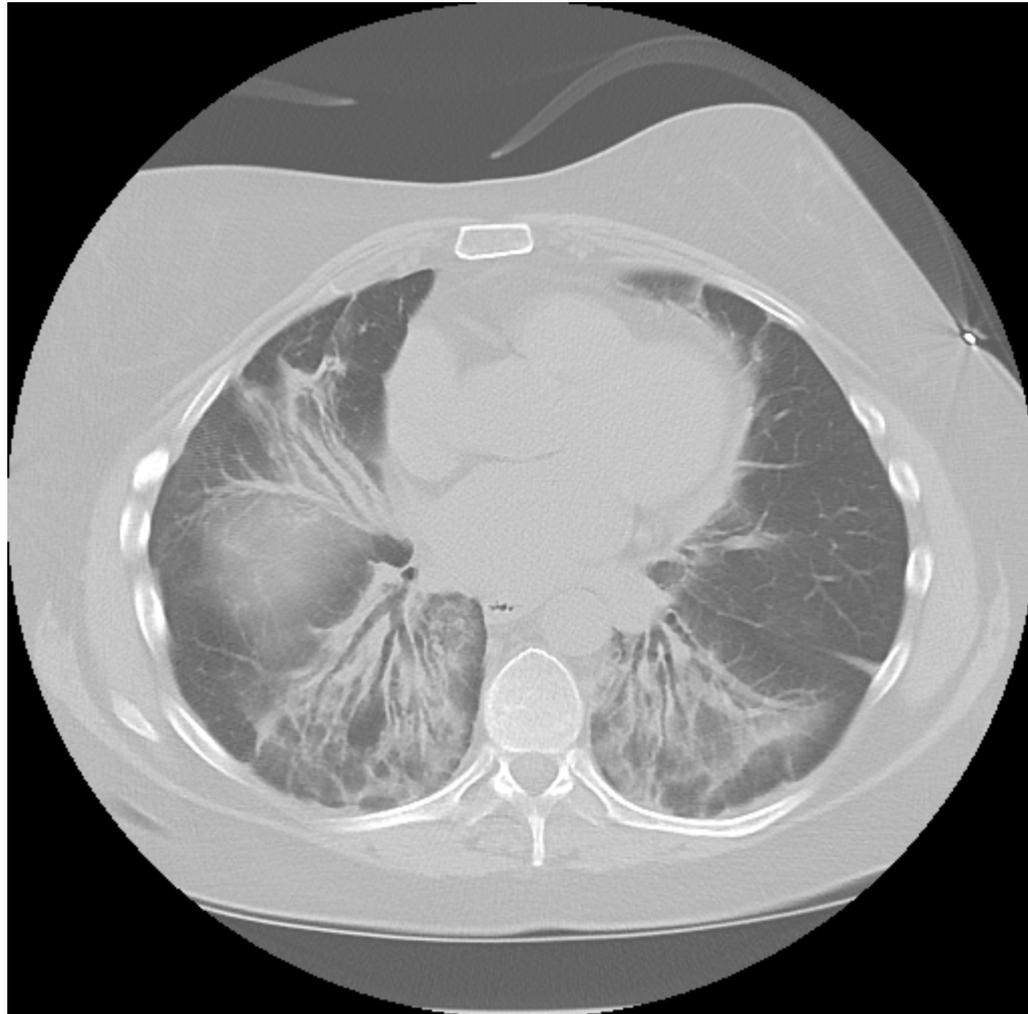
Treatment of Sarcoidosis

- 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

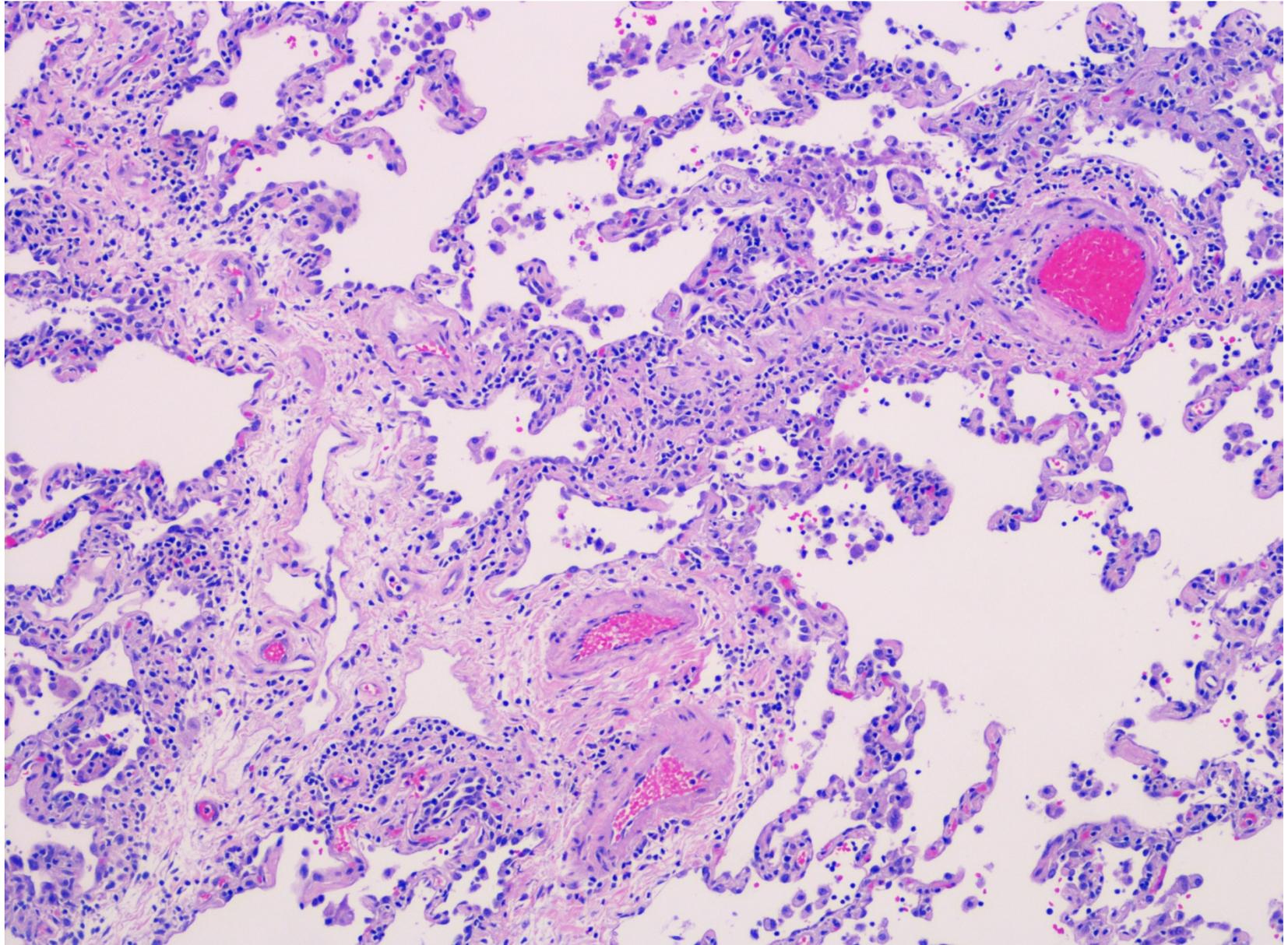
Revised ATS/ERS Idiopathic Interstitial Pneumonia Classification

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

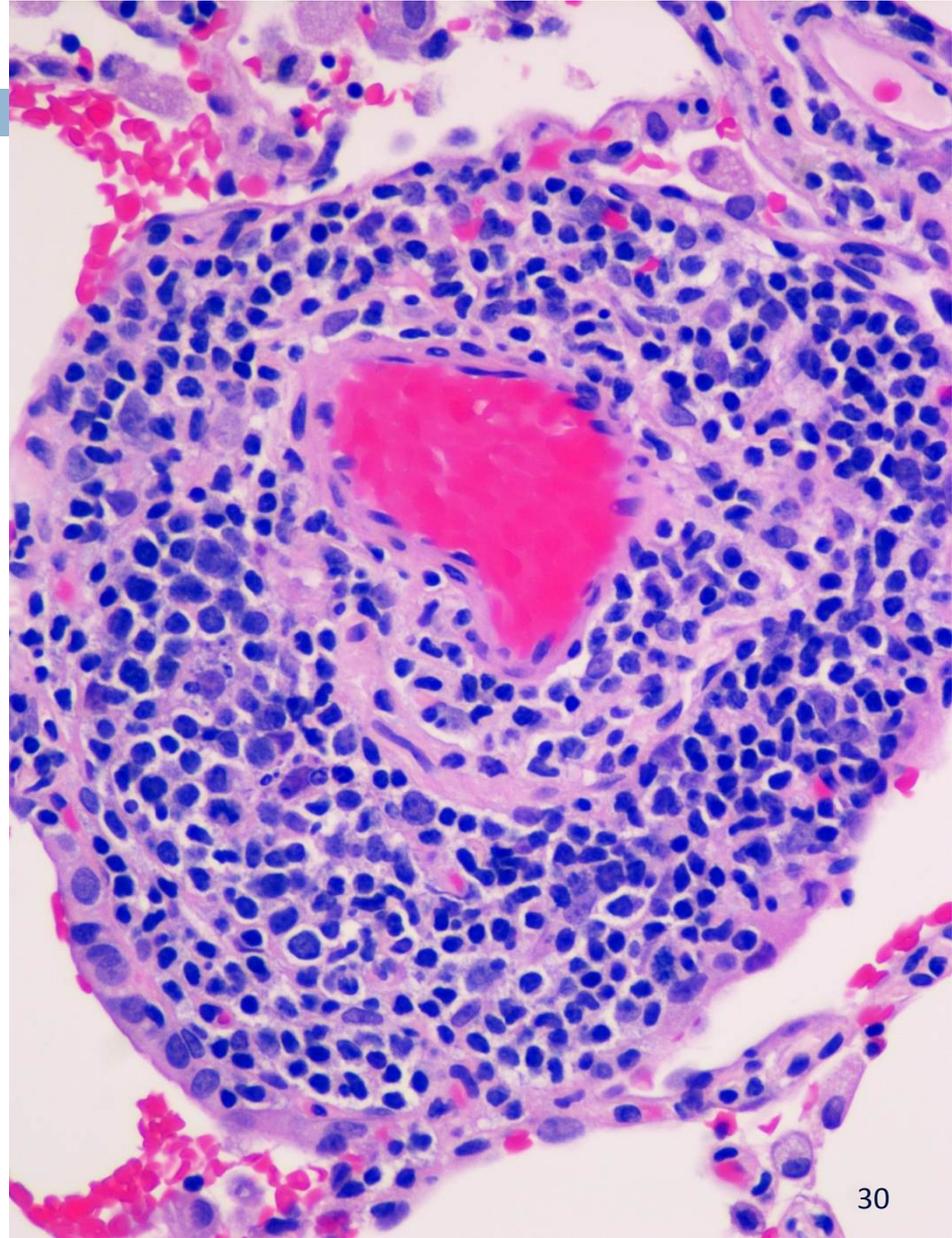
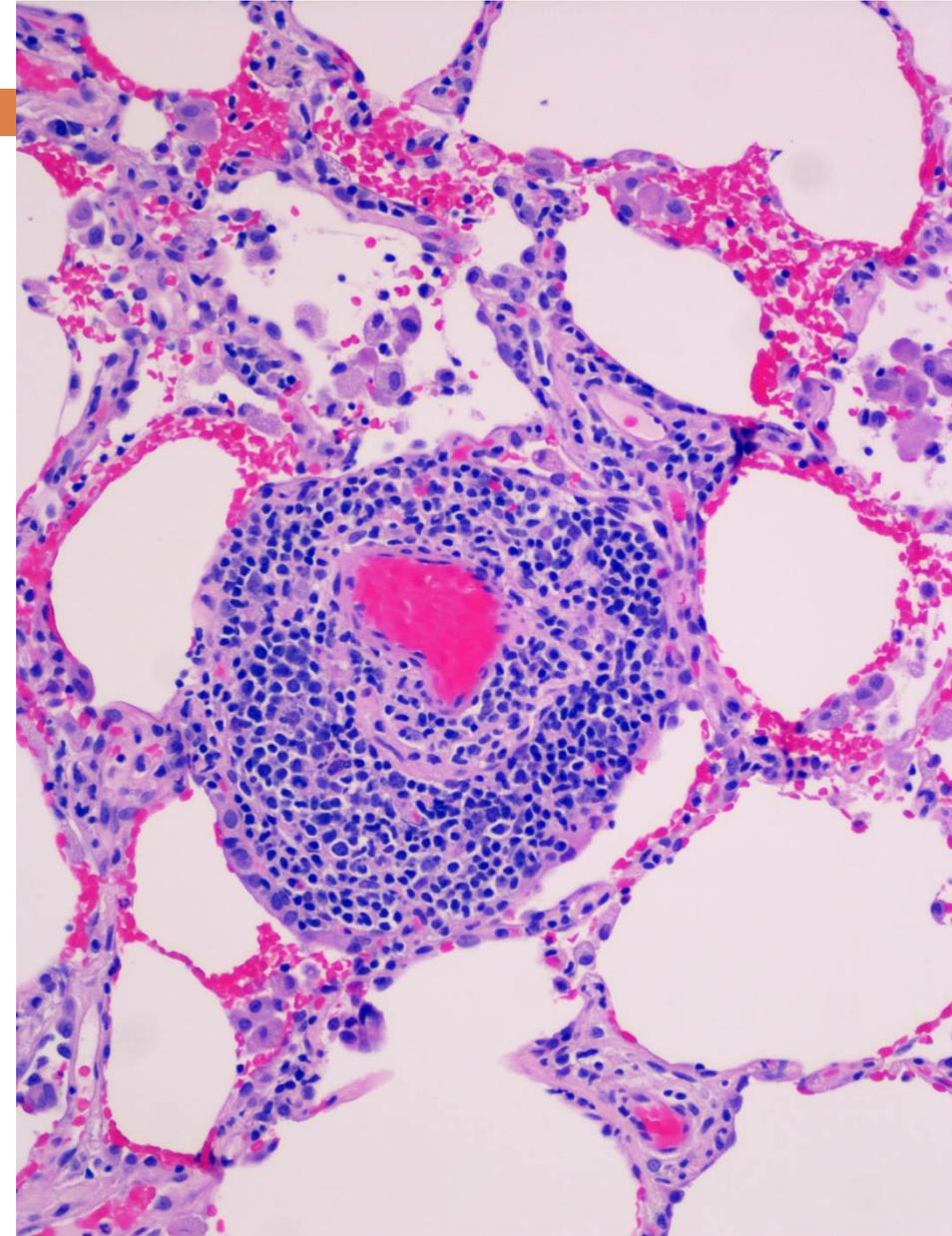
NSIP



RML – adjacent mild cellular IP



RLL – venulitis

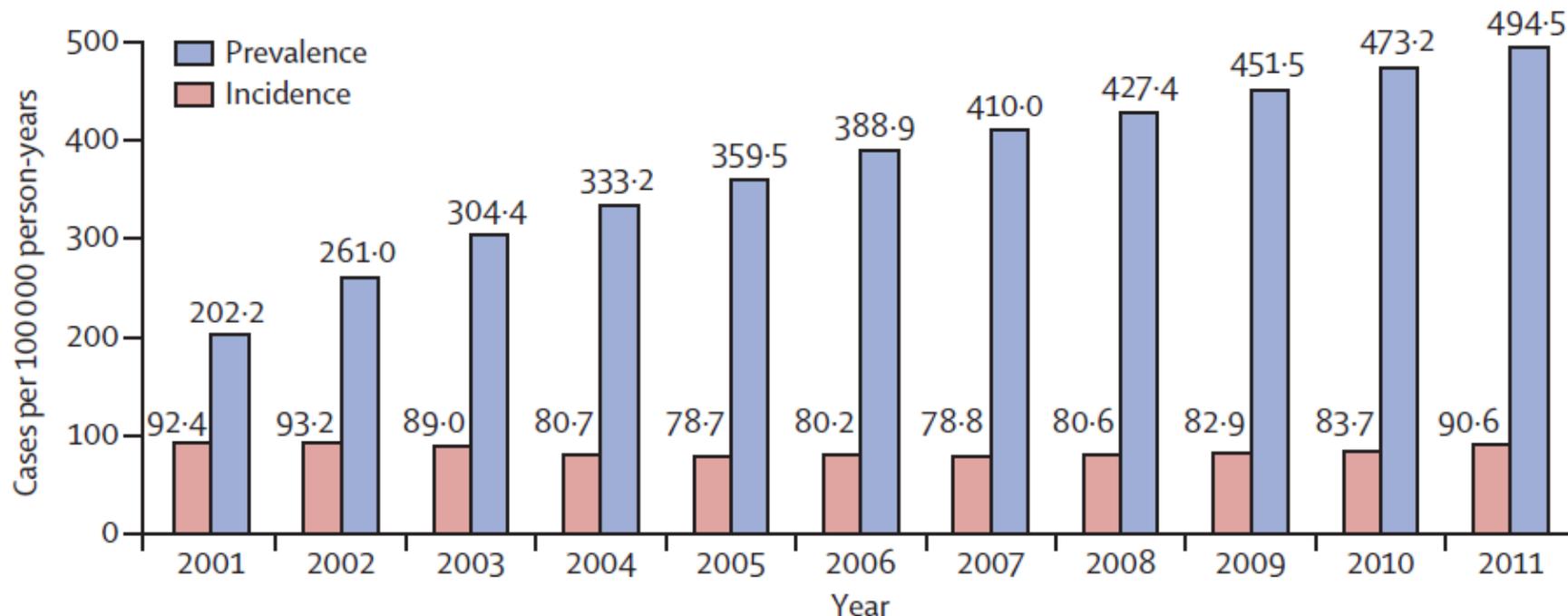


Current Definition of IPF

- 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 ≥ 65 y



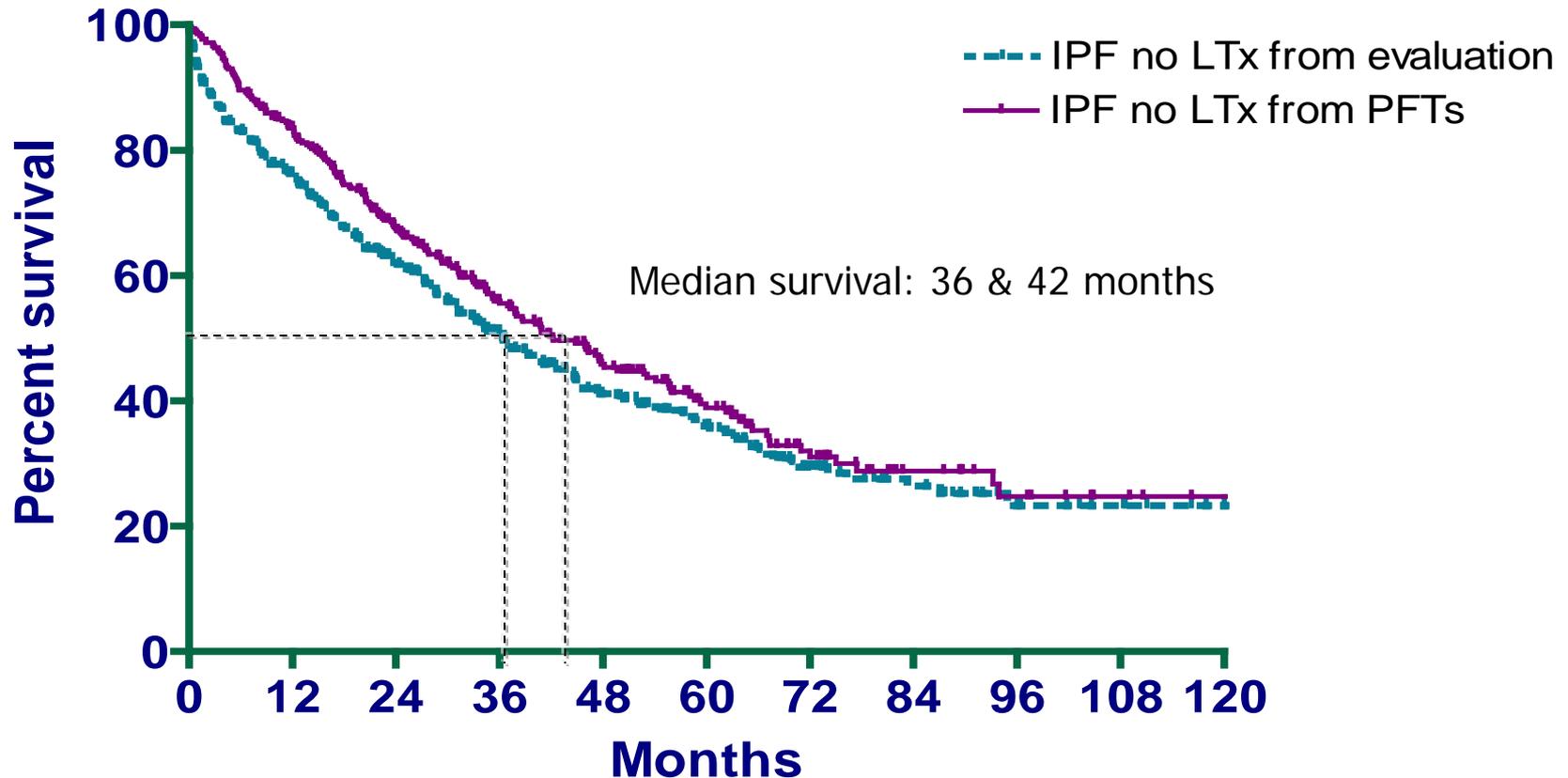
Factors associated with lower survival

- Age, index year, male gender

Median survival = 3.8 y

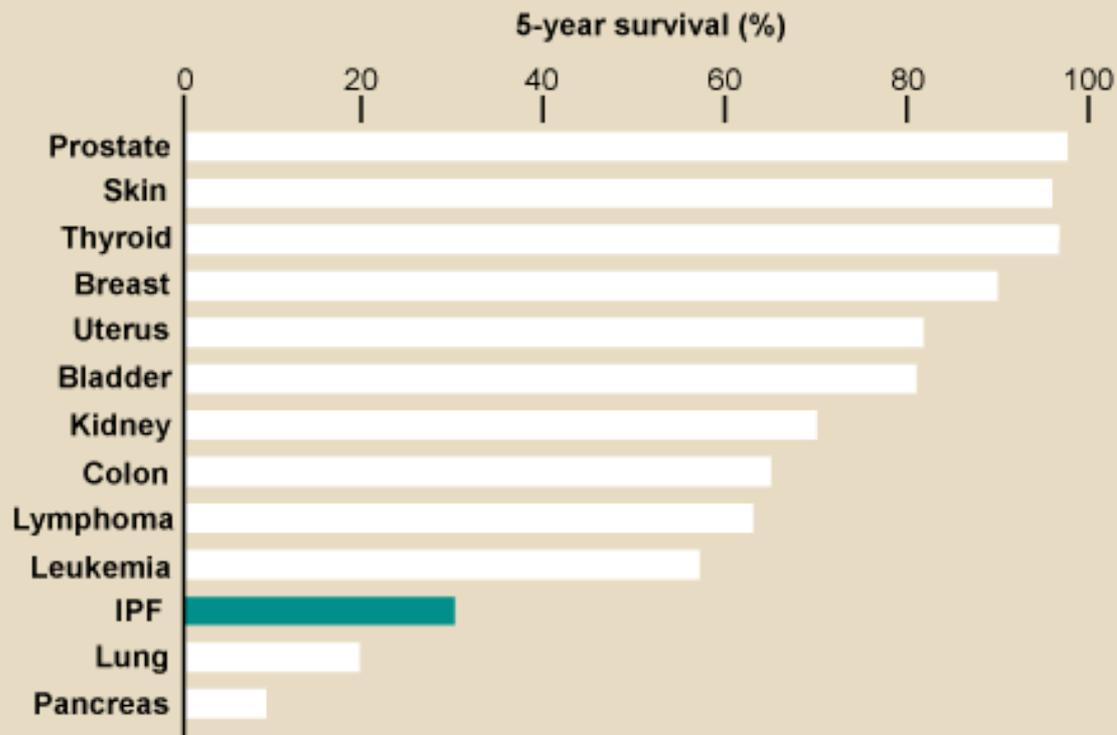
IPF: Survival at the Turn of the Century

2000-2009 (N=521)



Mortality Rate High in IPF

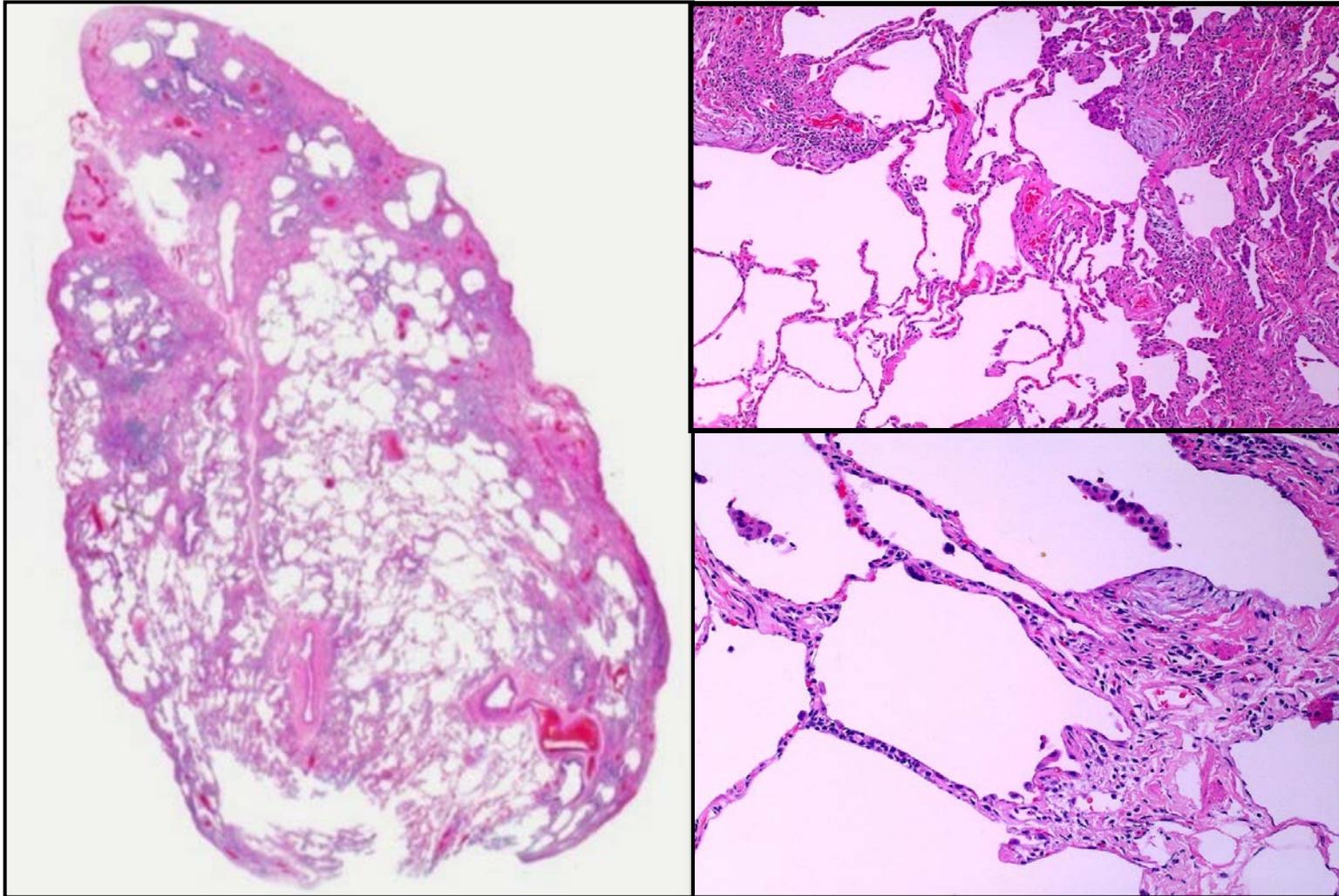
- 5 year survival rate (USA) is only 20-40%⁷
- Worse survival rates than many common cancers

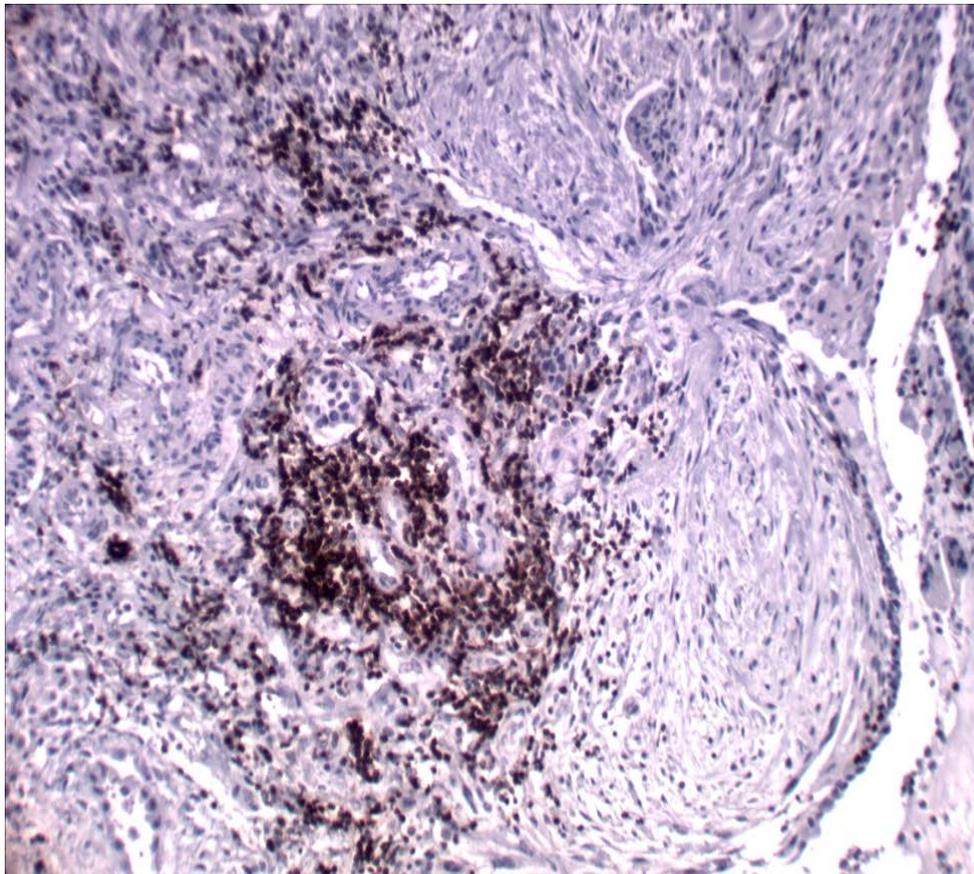


Reprinted with permission from Vancheri et al., Eur Respir J 2010⁷

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





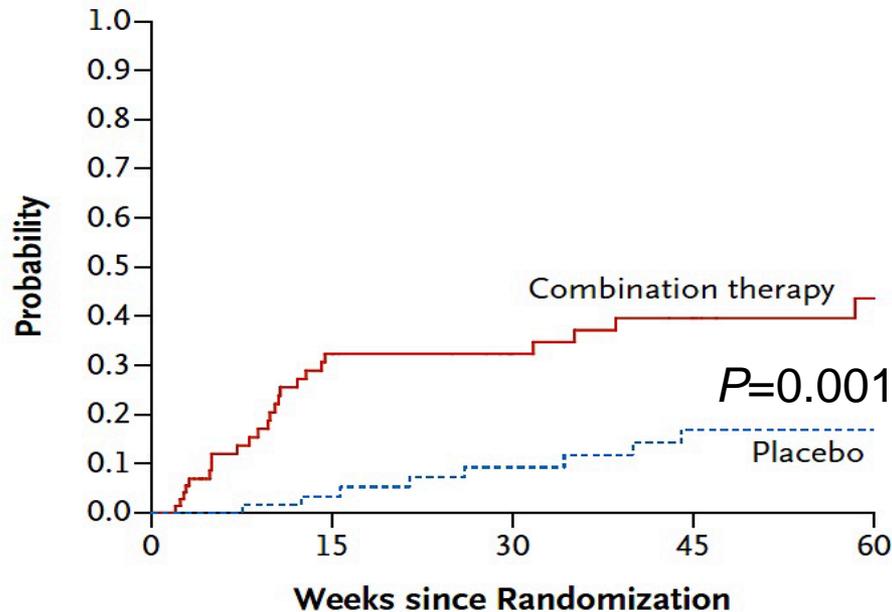
T-cells in IPF Lungs. Immunohistochemical staining shows that abnormal CD3⁺ T-cell infiltrates (black cells near arrow) in lungs of IPF patients with usual interstitial pneumonia are distributed heterogeneously, and are often especially prominent in proximity to fibroproliferative foci (star).

These infiltrates include both CD4⁺ and CD8⁺ 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

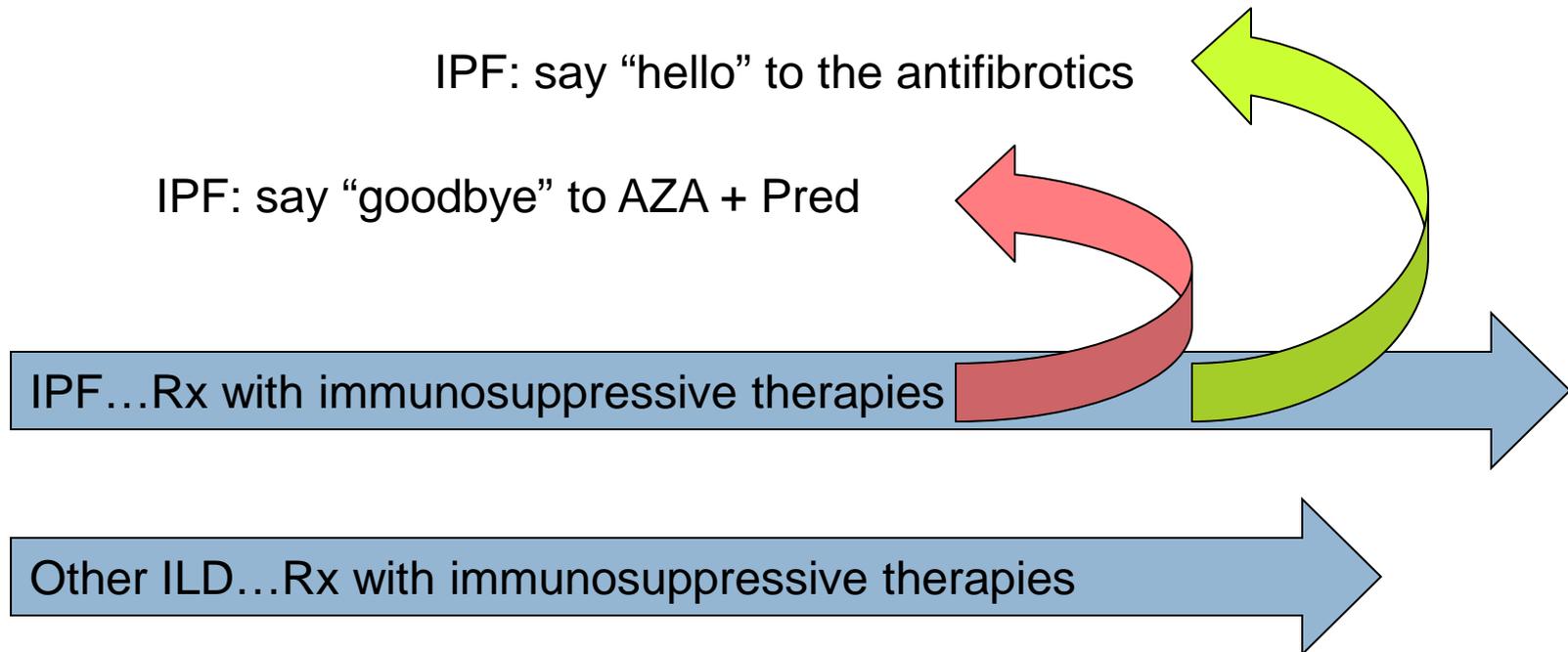


No. at Risk

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

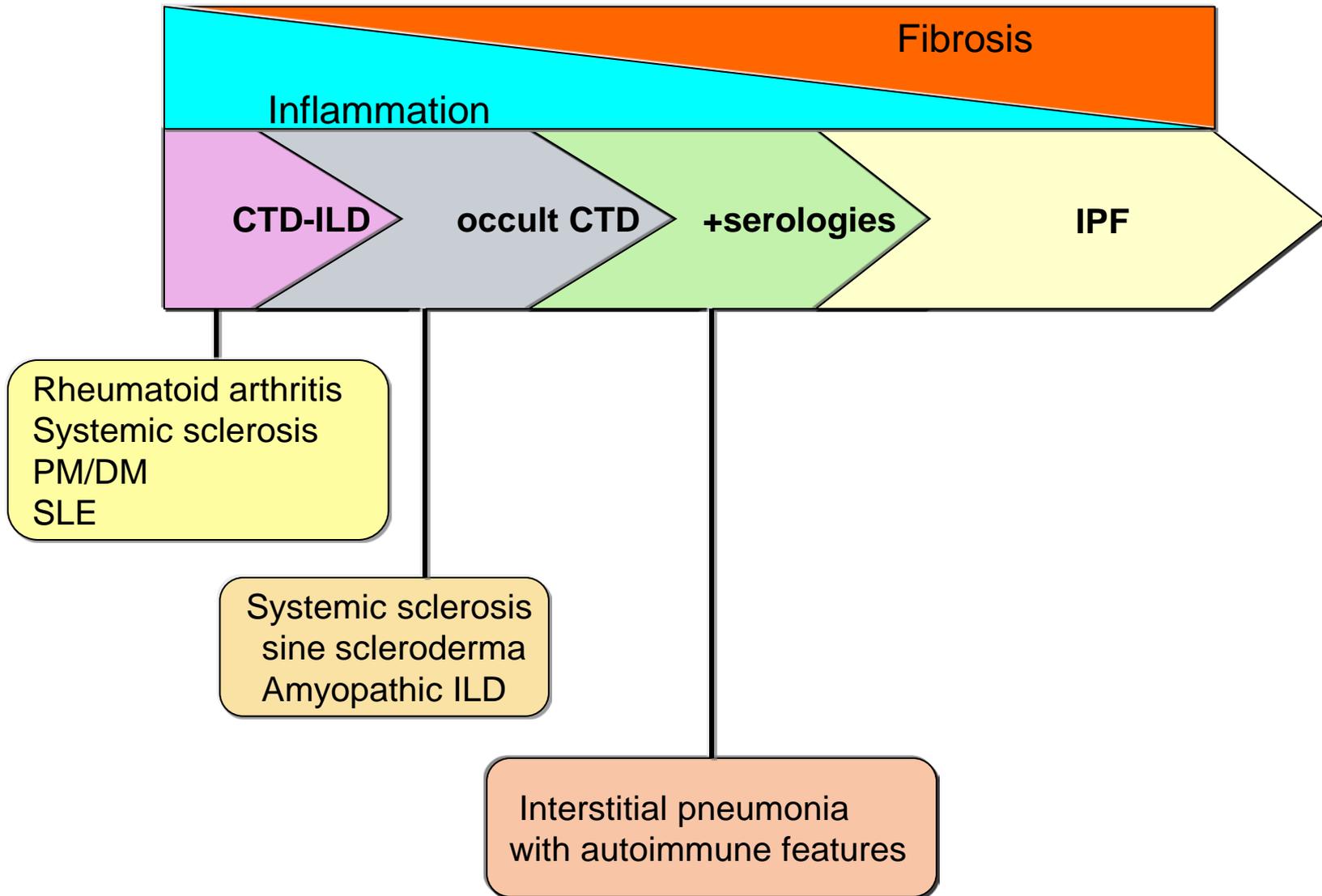
VOL. 370 NO. 22

Efficacy and Safety of Nintedanib in Idiopathic
Pulmonary Fibrosis

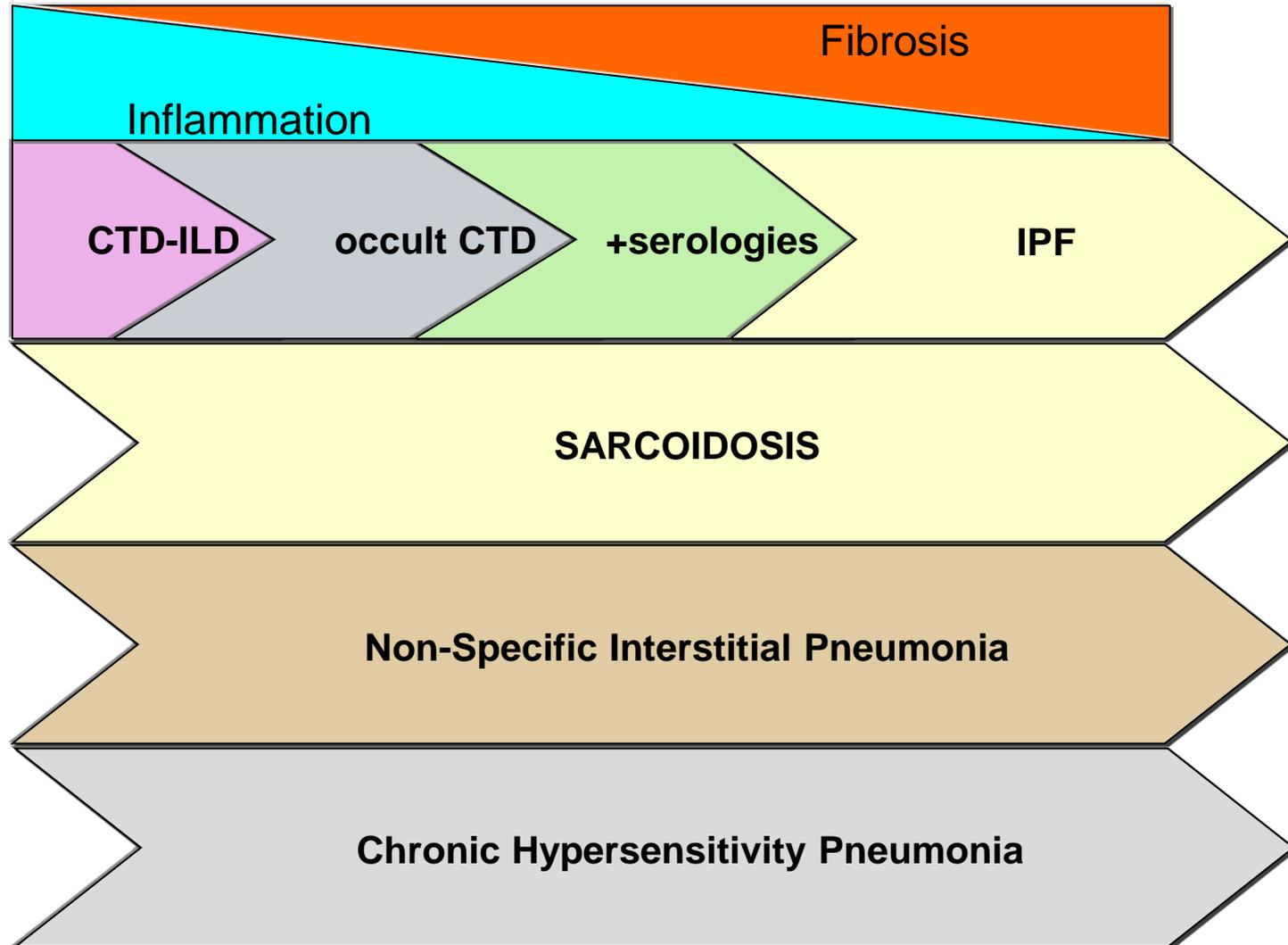
King TE Jr., et al. *N Engl J Med.* 2014;370:2083-2092.

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

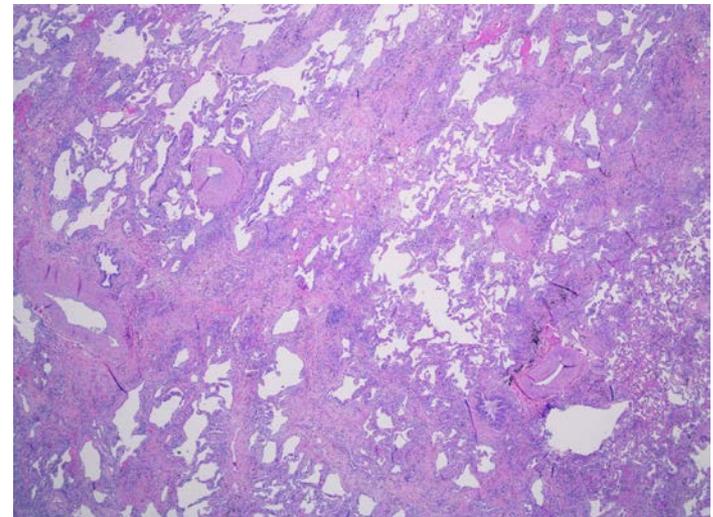
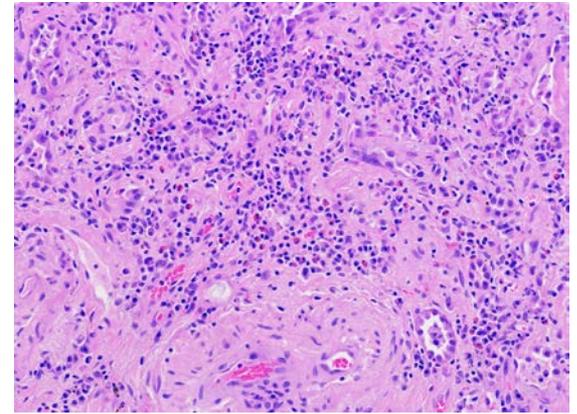
INTERSTITIAL LUNG DISEASE: A SPECTRUM

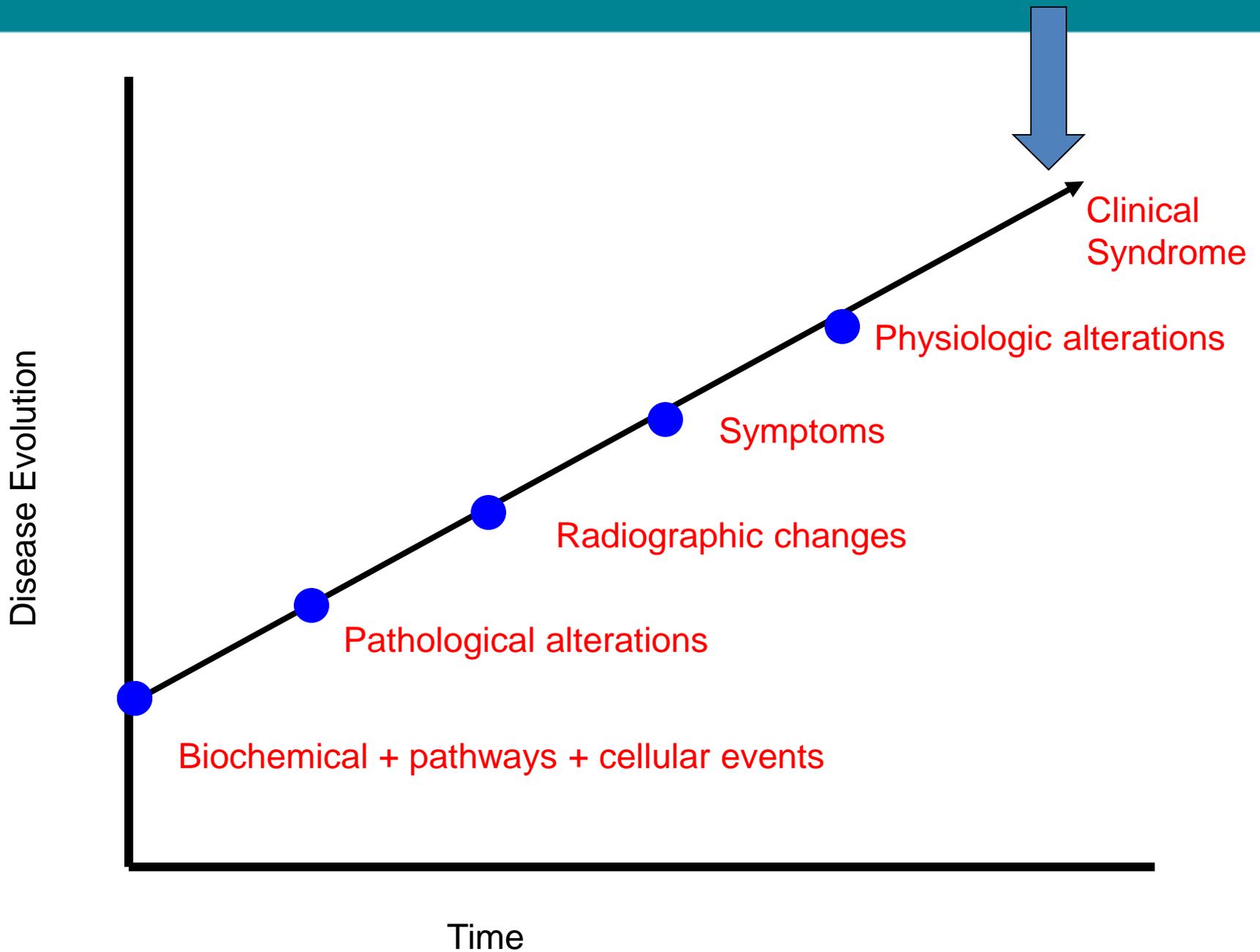


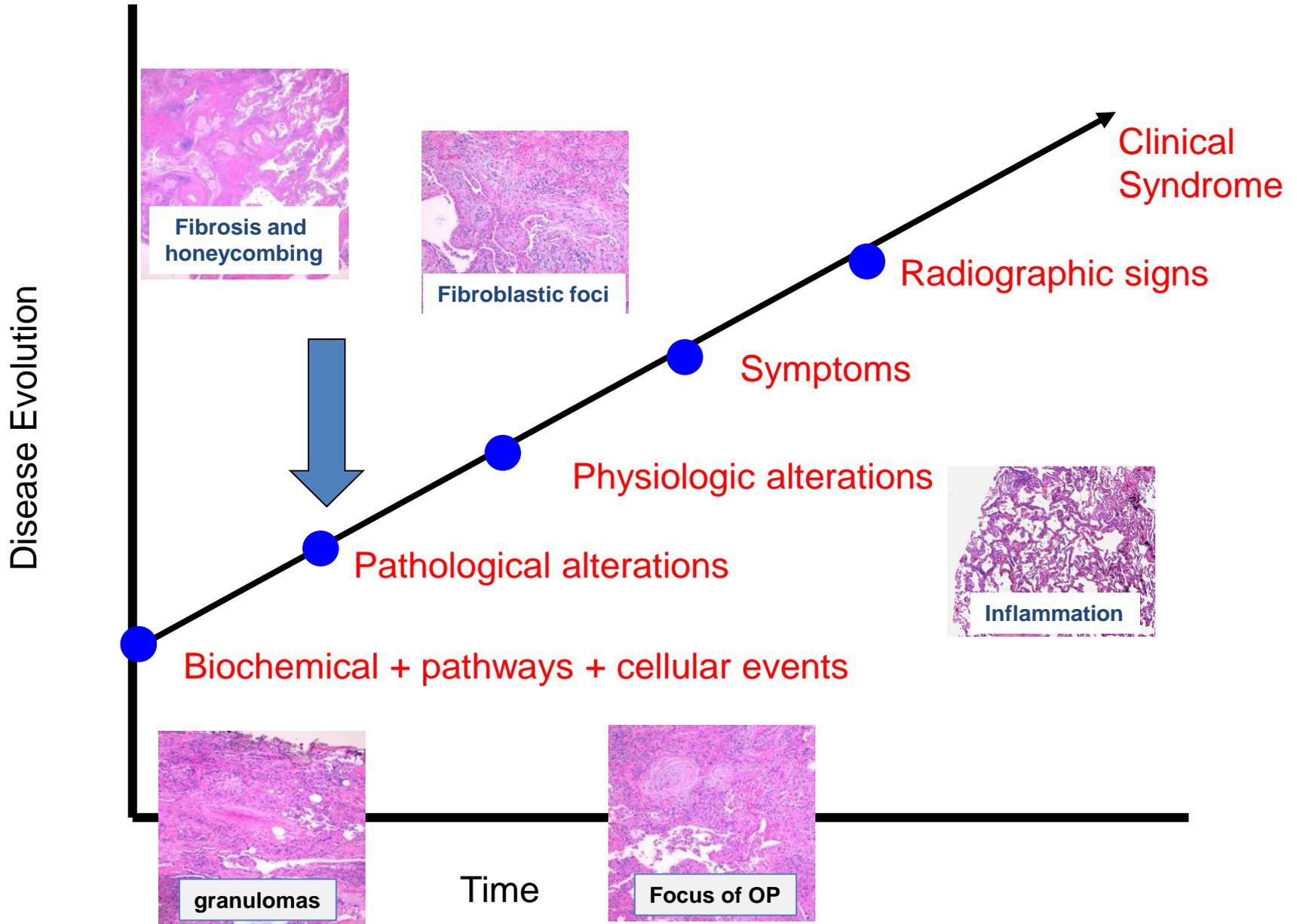
INTERSTITIAL LUNG DISEASE: A SPECTRUM



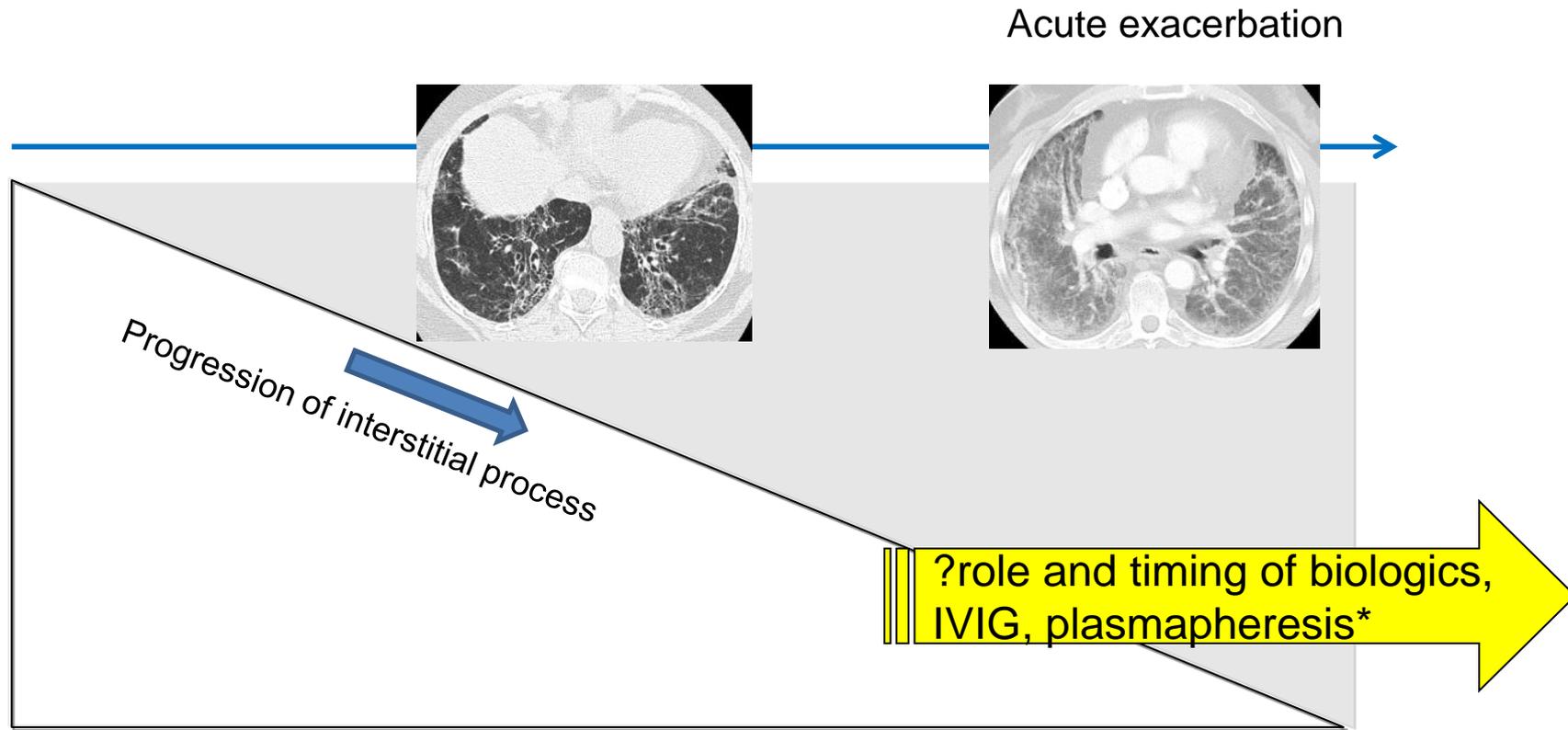
Same Case with Differing Pathology



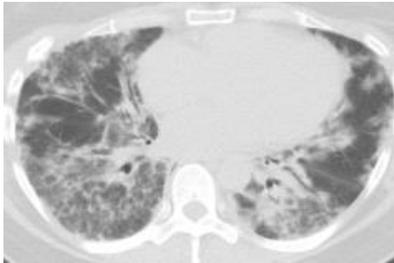




CTD-ILD: conceptual framework for future therapeutic approach



Therapy ||| ImmunoRx



||| ?antifibrotic*

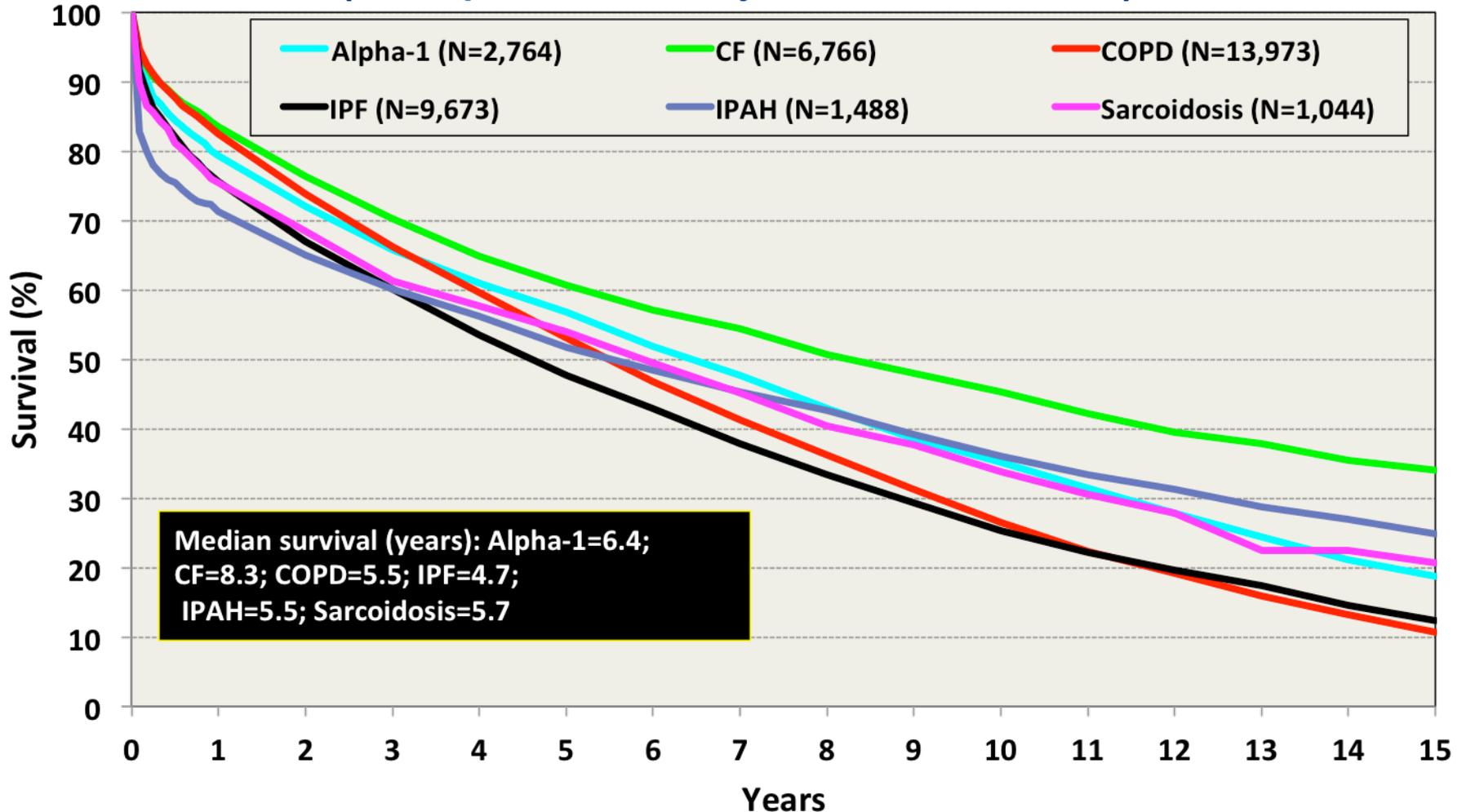
*not recommended, await RCT evidence

||| ?PAH therapy *

Adult Lung Transplants

Kaplan-Meier Survival by Diagnosis

(Transplants: January 1990 – June 2012)

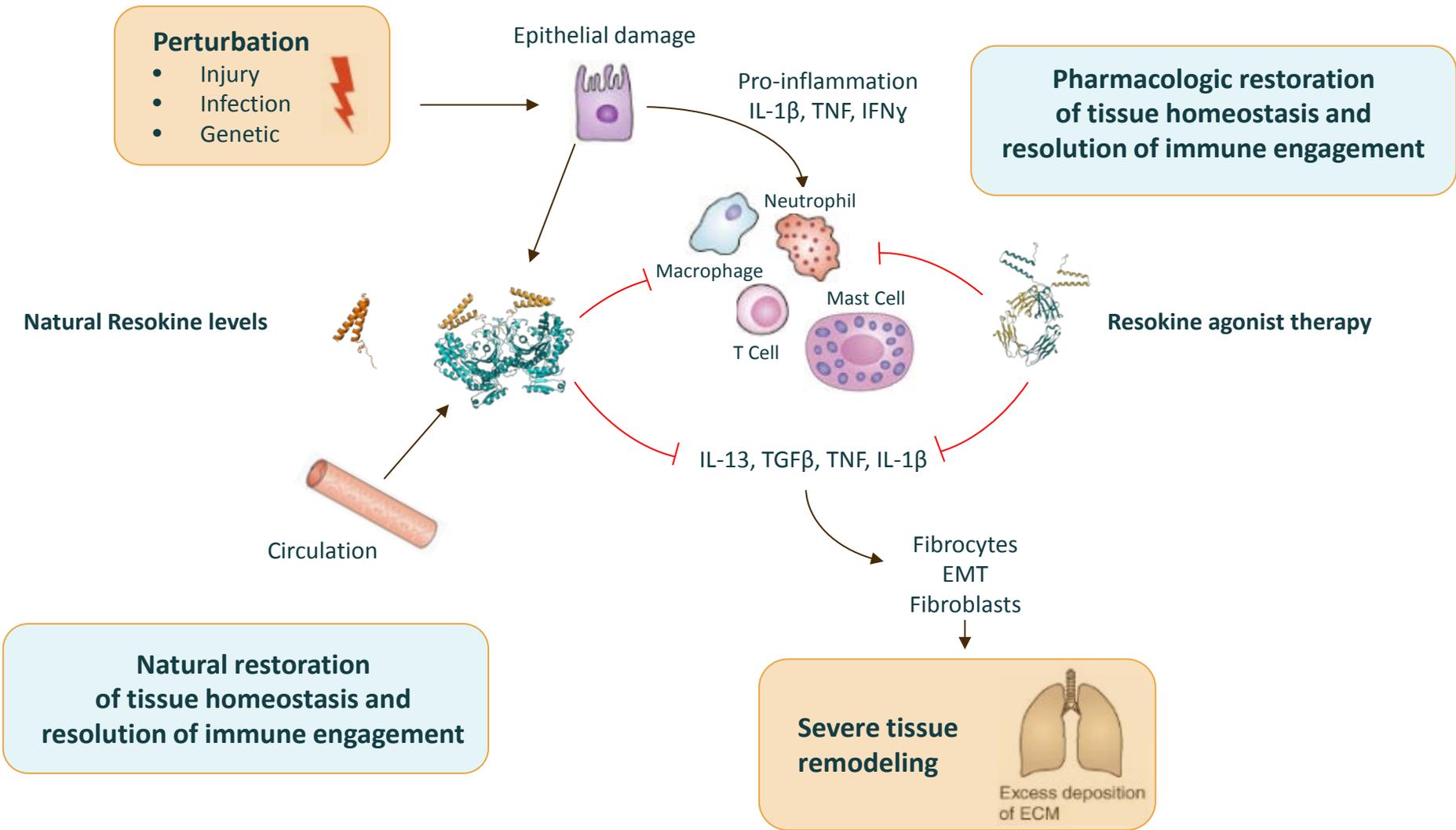




iMod.Fc Program

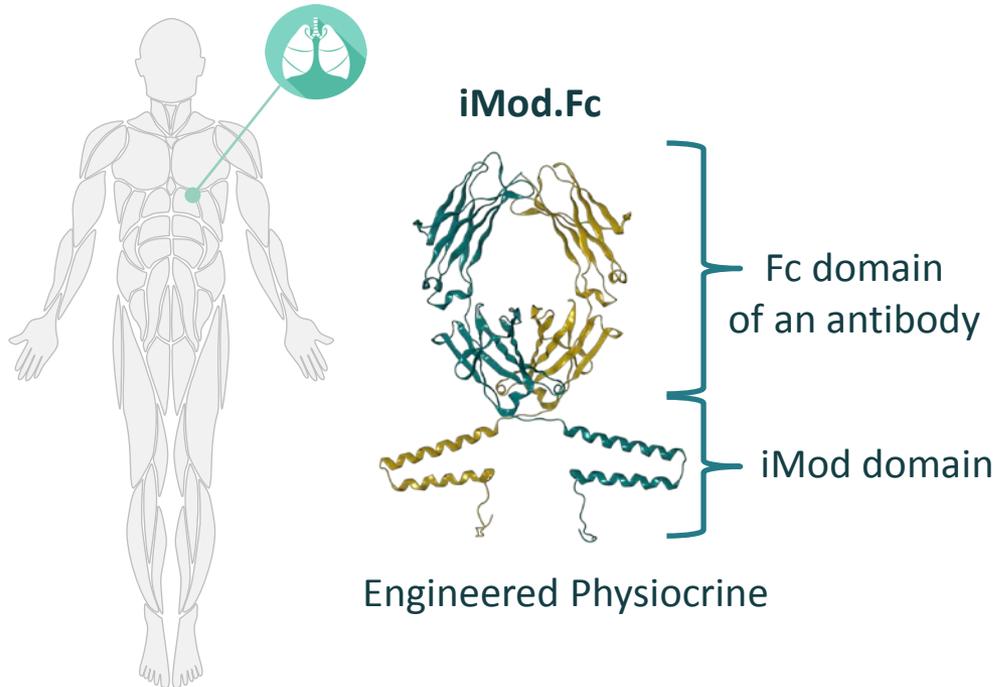
Lung Physiocrine Engineered to Treat Multiple Pulmonary Diseases

Resokine Promotes Lung Homeostasis



iMod.Fc Overview

Opportunity for Lung Patients



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

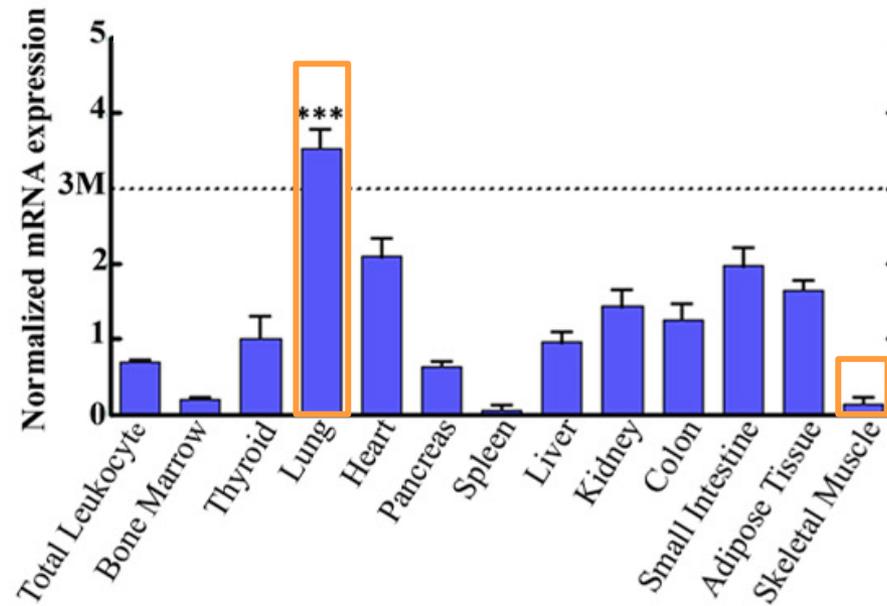
Fc domain: increased exposure to potentially enable **once-monthly dosing in humans**

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

1st molecule from internal Fc platform

iMod Domain in Lung

Splice Variant Express Data for iMod in Lung

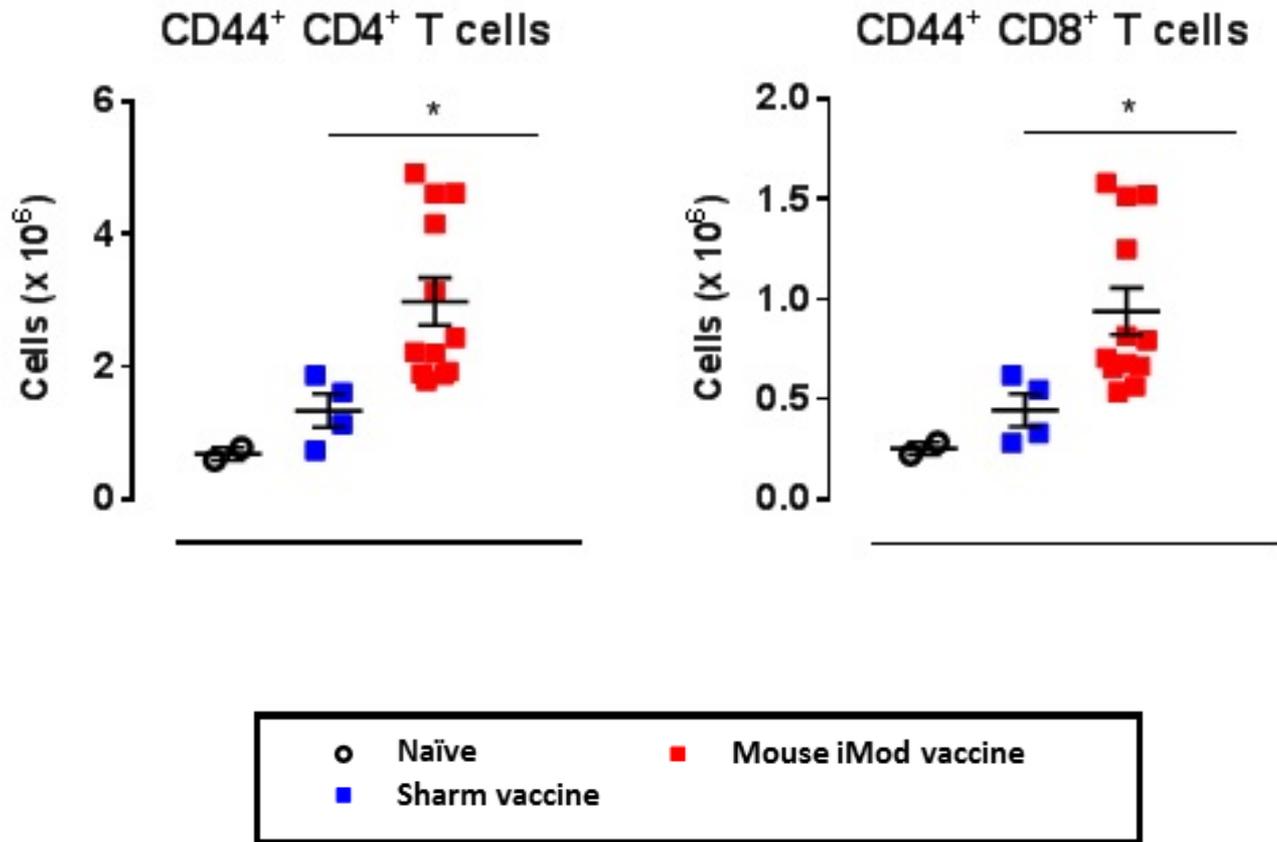


Splice variant for the **iMod domain** is relatively more expressed in **lung** than other tissues

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

Rodent functional knockout inducing idiopathic pulmonary disease using Bleomycin

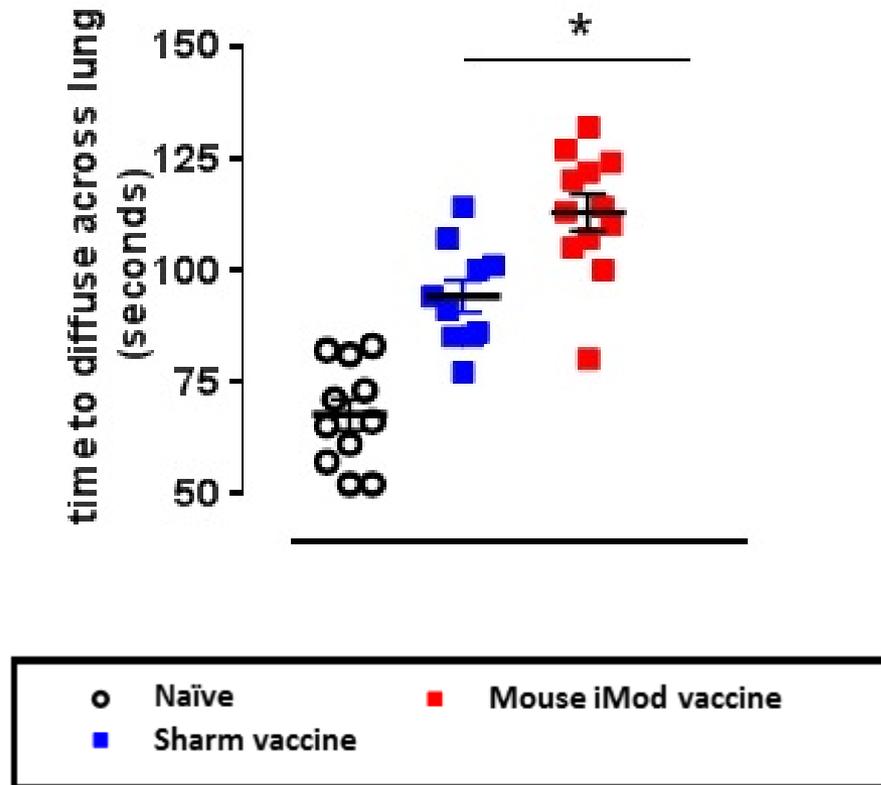
T cell Invasion



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

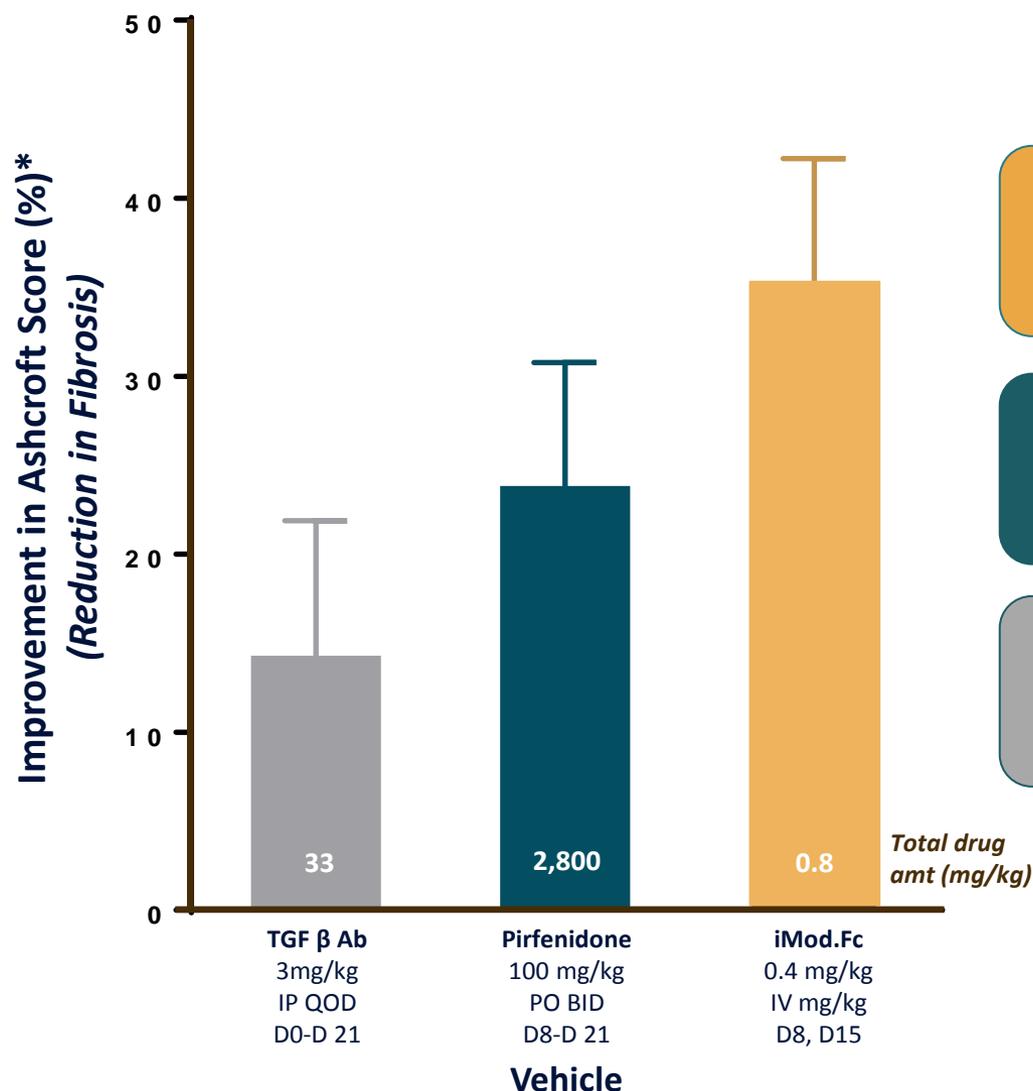
Rodent functional knockout inducing idiopathic pulmonary disease using Bleomycin

Impairment of lung function



iMod.Fc (Resokine Pathway) Outperforms Current Treatments

Established Rodent Model for Idiopathic Pulmonary Fibrosis (IPF)



Superior activity
in established IPF fibrotic model

iMod.Fc outperformed
pirfenidone at 1/3500th total dose

Two doses of iMod.Fc
outperformed 11 TGF β Ab doses

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?