UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

May 23, 2017
Date of Report (Date of earliest event reported)

ATYR PHARMA, INC.
(Exact name of registrant as specified in its charter)

Delaware	**001-37378**	**20-3435077**
(State or other jurisdiction of incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**

3545 John Hopkins Court, Suite #250
San Diego, California 92121

(Address of principal executive offices, including zip code)

(858) 731-8389

(Registrant's telephone number, including area code)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligations of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 or Rule 12b-2 of the Securities Exchange Act of 1934.

Emerging growth company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☒

Item 7.01 Regulation FD Disclosure.

aTyr Pharma, Inc. (the "Company") is participating at the American Thoracic Society's (ATS) 113 th International Conference to be held May 19 – 24, 2017 in Washington D.C. and will be presenting two poster presentations at such conference. The posters are titled "Resokine Modulates Immune Cell Infiltration into the Lung and Provides Therapeutic Activity in a Bleomycin-Induced Lung Fibrosis Model," to be presented on May 23, 2017, and "The Resokine Pathway is Implicated in the Pathology of Interstitial Lung Disease," to be presented on May 24, 2017. These posters are attached hereto as Exhibit 99.1 and Exhibit 99.2, respectively.

In conjunction with the ATS poster presentations, the Company will host an educational webinar on Tuesday, May 23, 2017 at 8:30 a.m. ET featuring Steven D. Nathan, M.D., FCCP, Director of the Advanced Lung Disease Program and Medical Director of the Lung Transplant Program at Inova Fairfax Hospital, to provide disease education on interstitial lung diseases that are characterized by an immune or fibrotic component. The Company will also provide an overview of the iMod.Fc program (Stalaris) in development for the potential treatment of patients with severe, rare pulmonary diseases characterized by an immune or fibrotic component for whom there are limited treatment options. A copy of the presentation materials for such educational webinar is attached hereto as Exhibit 99.3. The Company does not undertake to update the presentation materials.

The information under this Item 7.01, including Exhibits 99.1, 99.2 and 99.3 hereto, is being furnished and shall not be deemed "filed" for the purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liabilities of that section, nor shall such information be deemed incorporated by reference into any filing under the Securities Act of 1933, as amended, or the Exchange Act, except as expressly set forth by specific reference in such filing.

Item 9.01 Exhibits.

(d) Exhibits.

99.1	Poster presentation titled "Resokine Modulates Immune Cell Infiltration into the Lung and Provides Therapeutic Activity in a Bleomycin-Induced Lung Fibrosis Model."
99.2	Poster presentation titled "The Resokine Pathway is Implicated in the Pathology of Interstitial Lung Disease."
99.3	Educational Webinar Materials of aTyr Pharma, Inc. dated May 23, 2017.

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

ATYR PHARMA, INC.

By: /s/ John T. Blake
John T. Blake
Senior Vice President, Finance

Date: May 23, 2017

INDEX TO EXHIBITS

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A6428

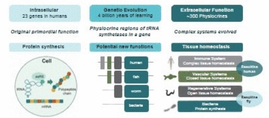
Resokine Modulates Immune Cell Infiltration Into the Lung and Provides Therapeutic Activity in a Bleomycin-induced Lung Fibrosis Model

K.M. Ogilvie, M.T. Do, K.P. Chiang, R.A. Adams, S.P. Crampton, L.A. Nangle, A.B. Cubitt, J.C. McKew, M.A. Ashlock, J.D. Mendlein
aTyr Pharma, San Diego, CA, USA

Exhibit 99.1

Introduction and Rationale

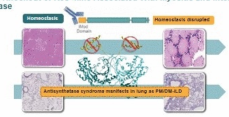
Physiocrines: Novel, Primal Extracellular Signaling Regions



During the evolution of complex organisms, aminoacyl-tRNA synthetases (AARS) acquired new domains without an intracellular enzymatic role. A number of these domains, as well as AARS proteins, possess extracellular activities and play important roles in homeostasis[1]. Histidyl-tRNA synthetase (HARS) and its splice variants exhibit extracellular activities, which are referred to as the Resokine pathway.

[1]Lo et al. Human tRNA Synthetase Catalytic Nulls with Diverse Functions. *Science*, 2014.

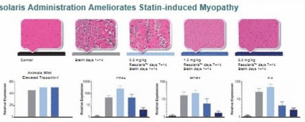
Functional Knockout of Resokine Associated With Myositis and Interstitial Lung Disease



Patients with auto-antibodies specific for Resokine (Jo-1) have notable T-cell infiltration particularly into muscle and lung tissues, which may manifest as susceptibility to myositis and interstitial lung disease (ILD). Therefore, blocking of potential immunomodulatory functions of Resokine may be particularly important in these diseases.

DM, dermatomyositis; PM, polymyositis.

Resolaris Administration Ameliorates Statin-induced Myopathy

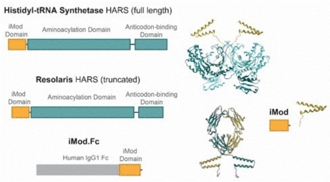


Myopathy was induced in female Sprague Dawley rats with 1 mg/kg cerivastatin administered daily for 7 days and then every other day until termination (Day 15). Resolaris was administered daily from days 7–14. Terminal histology (hemotoxylin and eosin), serum troponin I, and muscle mRNA expression data are shown.

Hypothesis: Administration of Resokine proteins may ameliorate lung disease

Methods

Resokine Proteins

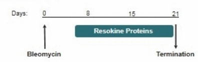


Molecule	Dose (mg/kg)	C_0 (ng/mL)	Vd (mL/kg)	CL (mL*h/kg)	$T_{1/2}$ (h)	AUC_{inf} (ng*h/mL)
iMod	8	145,455	119	574	0.5	13,944
Resolaris	10	97,774	128	75	2.5	13,491
iMod.Fc	10	1,407,553	265	1.8	94	633,937

Proteins used in these experiments are depicted above. The endogenous Physiocrine, Resokine, is synonymous with endogenous extracellular histidyl-tRNA synthetase (HARS). The domain structure is represented top left, whereas the 3-dimensional structure is represented top right. Resolaris is a recombinant version of the natural protein expressed in *E. coli* (middle domain structure) with a slightly truncated C-terminus. In some experiments, the mouse version of Resolaris (mResolaris) was used. The immunomodulatory domain (iMod) is represented to the right. iMod.Fc is represented in the lower left (primary domain structure) and far right (3-dimensional model). PK parameters obtained in Sprague Dawley rats are shown in the table.

AUC_{inf}, area under the curve extrapolated to infinity; C_0, initial concentration; CL, clearance; PK, pharmacokinetics; $T_{1/2}$, half-life; Vd, volume of distribution.

General Experimental Methods



C57Bl/6 mice received a single administration of saline (non-diseased control) or bleomycin (2-3 U/kg) intratracheally. Bleomycin-induced animals received Resokine proteins or Vehicle administered intravenously at dose levels and frequencies shown in the figure legends from Day 8 through termination. Anti-TGFβ antibody-, pirfenidone-, nintedanib-, or dexamethasone-treated groups were included for comparison.

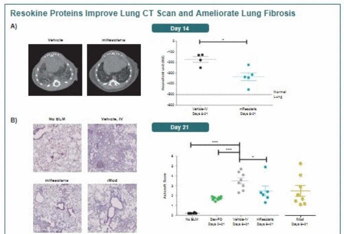
All animals were weighed and evaluated for respiratory distress daily. CT scans were conducted in one experiment. Mice were euthanized on Day 21 and tissues collected, stained, and evaluated for fibrosis and other histological changes by trained personnel who were blind to treatment conditions.

Data are expressed as mean ± SEM.

CT, computed tomography; TGF, transforming growth factor.

Results

Resokine Proteins Improve Lung CT Scan and Ameliorate Lung Fibrosis

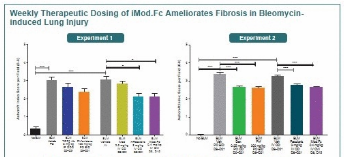


A) The first 5 animals from groups treated with Vehicle IV or mResolaris (3 mg/kg) were subject to computed tomography (CT) scan on Day 14 (i.e., after 1 week of protein treatment). Hounsfield units were measured from 8 regions of interest (ROI) selected at 2 anatomical planes from the series of ~100 images per animal. The 8 ROIs were averaged for each animal and are represented on the graph. Note that BLM causes an increase in Hounsfield units and mResolaris treatment reduces it toward normal (*p < 0.05, Student's t test).

B) Lung tissues collected on Day 21 (i.e., after 2 weeks of protein treatment) were stained with Masson's Trichrome stain. Ashcroft scores were assigned to 20 fields per animal and averaged. BLM induced an increase in fibrosis. mResolaris (3 mg/kg IV) and dexamethasone (0.25 mg/kg PO) significantly ameliorated fibrosis as measured by histological Ashcroft scoring (*p < 0.05; ***p < 0.001 vs. Vehicle IV. One-way ANOVA followed by Dunnett's post hoc test). iMod (2.5 mg/kg IV) treated samples did not reach statistical significance.

BLM, bleomycin; PO, per os, oral dosing.

Weekly Therapeutic Dosing of iMod.Fc Ameliorates Fibrosis in Bleomycin-induced Lung Injury



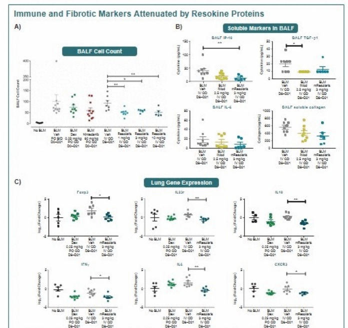
iMod.Fc administered therapeutically at 0.4 mg/kg QW drives efficacy comparable to or greater than pirfenidone, anti-TGFβ antibodies, and dexamethasone

Experiment 1: Lung tissues collected on Day 21 (i.e., after 2 weeks of protein treatment) were stained with Masson's Trichrome stain. Ashcroft scores were assigned to 8-10 fields per animal; all analyzed fields are represented. BLM induced an increase in histological fibrosis. mResolaris (3 mg/kg daily) and iMod.Fc (0.4 mg/kg once weekly) significantly ameliorated fibrosis as measured by histological Ashcroft scoring. iMod, TGFβ blockade and pirfenidone did not have significant effects on fibrosis (*p < 0.05; ***p < 0.001 vs. Vehicle IV, Kruskal-Wallis ANOVA followed by Tukey's post hoc test).

Experiment 2: Lung tissues collected on Day 21 (i.e., after 2 weeks of protein treatment) were stained with Masson's Trichrome stain. Ashcroft scores were assigned to 20 fields per animal; all analyzed fields are represented. BLM induced an increase in histological fibrosis. Resolaris (3 mg/kg daily) and iMod.Fc (0.4 mg/kg once weekly) significantly ameliorated fibrosis as measured by histological Ashcroft scoring (***p < 0.001 vs. Respective Vehicle, Kruskal-Wallis ANOVA followed by Tukey's post hoc test).

PO, per os, oral dosing.

Immune and Fibrotic Markers Attenuated by Resokine Proteins



A) Bronchiolar-alveolar lavage fluid (BALF) cell counts: At euthanasia, the lungs were flushed twice with phosphate-buffering saline (PBS) and fluid was collected. BALF was centrifuged, the erythrocytes were lysed, and the remaining cells were resuspended in PBS. After staining with trypan blue, cells were counted using a hemocytometer. Resolaris significantly decreased the number of immune cells present in the BALF. The number of cells counted was not significantly changed by dexamethasone or nintedanib in comparison to Vehicle PO (*p < 0.05; **p < 0.01 vs. Vehicle IV. One-way ANOVA followed by Dunnett's post hoc test).

B) Soluble markers in BALF: BALF supernatants were collected after centrifugation as described above and soluble markers measured using commercially available kits. Resokine proteins significantly decreased IP-10 and TGFβ, and a tendency for lowering was observed on several other immune and fibrotic markers, including IL-6 and soluble collagen (*p < 0.05; **p < 0.01 vs. Vehicle IV, Kruskal-Wallis ANOVA followed by Dunn's post hoc test).

C) Lung gene expression: A small sample of lung was collected, frozen, and subsequently processed to isolate RNA. PCR was conducted using the Fluidigm platform. mResolaris significantly decreased expression of several immune cell genes (*p < 0.05; **p < 0.01 vs. Vehicle IV, Student's t test).

PO, per os, oral dosing.

Conclusions

- The Resokine pathway is functional in the lungs of rodents.
- Therapy with Resokine proteins was efficacious and ameliorated bleomycin-induced lung fibrosis.
- Certain Resokine pathway proteins may be worthy of exploration for their therapeutic effects in human lung diseases, such as interstitial lung disease.

Acknowledgements

Scientists and study directors at Stelic MC, TNO, and Biomodels who conducted the experiments on aTyr Pharma's behalf.
aTyr scientists Kenny d'Arigo and Nicole Schultz who were responsible for PK analysis and PCR conduct, respectively.

Graphics support was provided by Oxford PharmaGenesis, Inc. and was funded by aTyr Pharma, Inc.

Disclosure

This study was funded by aTyr Pharma, Inc.

Presented at the American Thoracic Society International Conference; 19–24 May 2017; Washington, DC, USA.

#611

The Resokine Pathway Is Implicated in the Pathology of Interstitial Lung Disease

L.A. Nangle[1*], Y. Tong[2,3], E. Mertsching[1], S.P. Crampton[1], R.A. Adams[1], K.P. Chiang[1], K.M. Ogilvie[1], P. Schimmel[4], J.C. McKew[1], D. King[1], J.D. Mendlein[1]

[1]aTyr Pharma, San Diego, CA, USA; [2]Pangu Biopharma, Hong Kong, China; [3]AS HKUST – Scripps R&D Laboratory, Institute for Advanced Study, Hong Kong, China; [4]The Scripps Laboratories for tRNA Synthetase Research, The Scripps Research Institute, La Jolla, CA, USA

*Corresponding and presenting author: L.A. Nangle, lnangle@atyrpharma.com

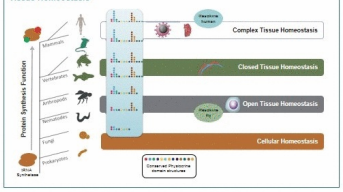
Exhibit 99.2

Rationale

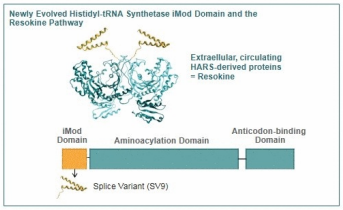
- The histidyl-tRNA synthetase (HARS) protein has long been identified as the sole target of Jo-1 autoantibodies (Jo-1 Abs), which are, in many cases, accompanied by interstitial lung disease (ILD). Extracellular HARS proteins (Resokine) are found in circulation at physiologically relevant levels in healthy individuals (~200 pM) and are greatly reduced in patients with Jo-1 Abs, leading us to investigate the source of Resokine and explore the possibility that insufficiency plays a role in the pathology of inflammatory myopathies and ILD associated with Jo-1 Abs.

Evolution-elaborated Physiological Systems for Homeostasis

Physiocrine Hypothesis: Physiological Modulation From Primordial Tissue Homeostasis

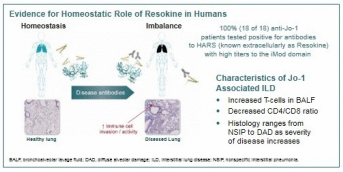


Newly Evolved Histidyl-tRNA Synthetase iMod Domain and the Resokine Pathway



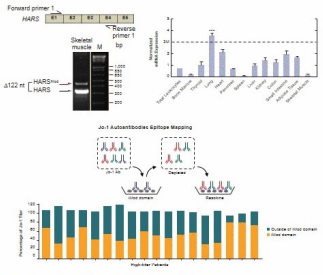
Disrupting the Resokine Pathway Promotes Lung Damage

Evidence for Homeostatic Role of Resokine in Humans



BALF, bronchoalveolar lavage fluid; DAD, diffuse alveolar damage; ILD, interstitial lung disease; NSIP, nonspecific interstitial pneumonia.

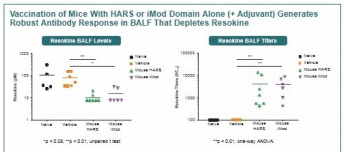
Resokine Splice Variant (SV9) Represents the iMod Domain, the Target of a High Percentage of Disease-linked Jo-1 Antibodies



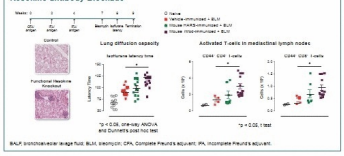
- The predominant epitopes are in the N-terminal iMod domain
- Additional epitopes are present throughout HARS, indicating epitope spreading has occurred

Pathological Remodeling of the Lung in a Model of Resokine Pathway Disruption

Vaccination of Mice With HARS or iMod Domain Alone (+ Adjuvant) Generates Robust Antibody Response in BALF That Depletes Resokine



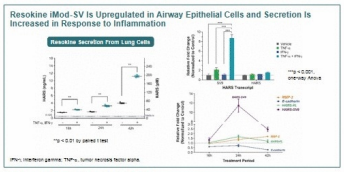
Exacerbated Response to Bleomycin-induced Injury in Mice With Resokine-antibody Blockade



BALF, bronchoalveolar lavage fluid; BLM, bleomycin; CFA, Complete Freund's adjuvant; IFA, incomplete Freund's adjuvant.

Regulation of Resokine Splice Variant in Inflammation

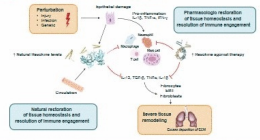
Resokine iMod-SV Is Upregulated in Airway Epithelial Cells and Secretion Is Increased in Response to Inflammation



IFNγ, interferon gamma; TNFα, tumor necrosis factor alpha.

Regulation of the Resokine Pathway in Lung Inflammation

Resokine Pathway Promotes Lung Homeostasis



Results

- We characterized serum from a number of Jo-1–positive patients and found the majority exhibited strong cross-reactivity with the N-terminal portion of Resokine and that a splice variant (SV9), which encodes only the N-terminal domain of the protein, is enriched in human lung tissue. Here, we demonstrate that in the lung-derived adenocarcinoma cell line A549, Resokine is actively secreted following stimulation with the inflammatory cytokines IFN-γ and TNF-α, two key players in the initiation of lung inflammation and fibrosis. Secretion is dose dependent and synergistic. SV9, but not the full-length mRNA, is increased following inflammatory cytokine stimulation and its peak expression precedes that of the secreted protein.
- Repeated vaccination of mice with murine Resokine in the presence of adjuvant can break tolerance and generate auto-antibodies. Resokine was present in bronchoalveolar lavage fluid of controls and undetectable in vaccinated animals. In animals with a high titer to Resokine, infiltration of immune cells (including T-cells) into skeletal muscle and lung was detected. Furthermore, in vaccinated animals receiving bleomycin intratracheally, lung function was more severely impacted and both CD4+ and CD8+ T-cells were increased in the mediastinal nodes. Interestingly, these pathologies were observed only in mice that carry a genetic mutation in dysferlin (and other loci) but not in wild-type mouse strains (e.g., C57bl/6).

Conclusion

- Immune invasion pathologies observed in mice forced to break tolerance to Resokine in the background of another tissue-damaging genetic mutation are similar to activity observed in patients with Jo-1 autoantibodies. This suggests that induction of Resokine insufficiency may disrupt immune homeostasis in a manner that manifests as pathological in lung and muscle. The findings that Resokine circulates at pM levels and the splice variant SV9 is synergistically induced and secreted by lung-derived cells in an inflammatory environment provide evidence for an extracellular niche in which autoantibodies could mediate neutralization of these proteins to induce pathology.

References

Zhou, J.J. et al. Secreted histidyl-tRNA synthetase splice variants elaborate major epitopes for autoantibodies in inflammatory myopathy. *J Biol Chem*. 2014.

Acknowledgements

Aline Ha (Jo-1 antibody analysis), Kenny D'Angiolillo Bruner (Resokine and Resokine-antibody analysis), Jeanette Arnquist (flow cytometry), Shiwen Xu, Cecil Lo, and Cecil Lau (experimental advice, primer design and testing, cell culture). Graphics support was provided by Oxford PharmaGenesis, Inc. and was funded by aTyr Pharma, Inc.

Disclosure

This study was funded by aTyr Pharma, Inc.

Presented at the American Thoracic Society International Conference; 19–24 May 2017; Washington, DC, USA.

Exhibit 99.3

aTyr Pharma
NASDAQ: LIFE

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

Forward-Looking Statements

The following slides and any accompanying oral presentation contain forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995 and other federal securities laws. The use of words such as "may," "might," "will," "should," "expect," "plan," "anticipate," "believe," "estimate," "project," "intend," "future," "potential," "opportunity," or "continue," and other similar expressions are intended to identify forward-looking statements. For example, all statements we make regarding the potential therapeutic benefits of Physiocrines and our product candidates, including Resolaris™ and our iMod.Fc program, the ability to successfully advance our pipeline or product candidates, the timing within which we expect to initiate, receive and report data from, and complete our planned clinical trials, and our ability to receive regulatory approvals for, and commercialize, our product candidates, our ability to identify and discover additional product candidates, our projected cash expenditures, and the ability of our intellectual property portfolio to provide protection are forward-looking statements. All forward-looking statements are based on estimates and assumptions by our management that, although we believe to be reasonable, are inherently uncertain. All forward-looking statements are subject to risks and uncertainties that may cause actual results to differ materially from those that we expected. These risks, uncertainties and other factors are more fully described in our filings with the U.S. Securities and Exchange Commission, including our most recent Quarterly Report on Form 10-Q, our Annual Report on Form 10-K and in our other filings. The forward-looking statements in this presentation speak only as of the date of this presentation and neither we nor any other person assume responsibility for the accuracy and completeness of any forward-looking statement. We undertake no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events or otherwise, except as required by law.

We own various U.S. federal trademark applications and unregistered trademarks, including our company name and Resolaris™. All other trademarks or trade names referred to in this presentation are the property of their respective owners. Solely for convenience, the trademarks and trade names in this presentation are referred to without the symbols ® and ™, but such references should not be construed as any indicator that their respective owners will not assert, to the fullest extent under applicable law, their rights thereto.

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

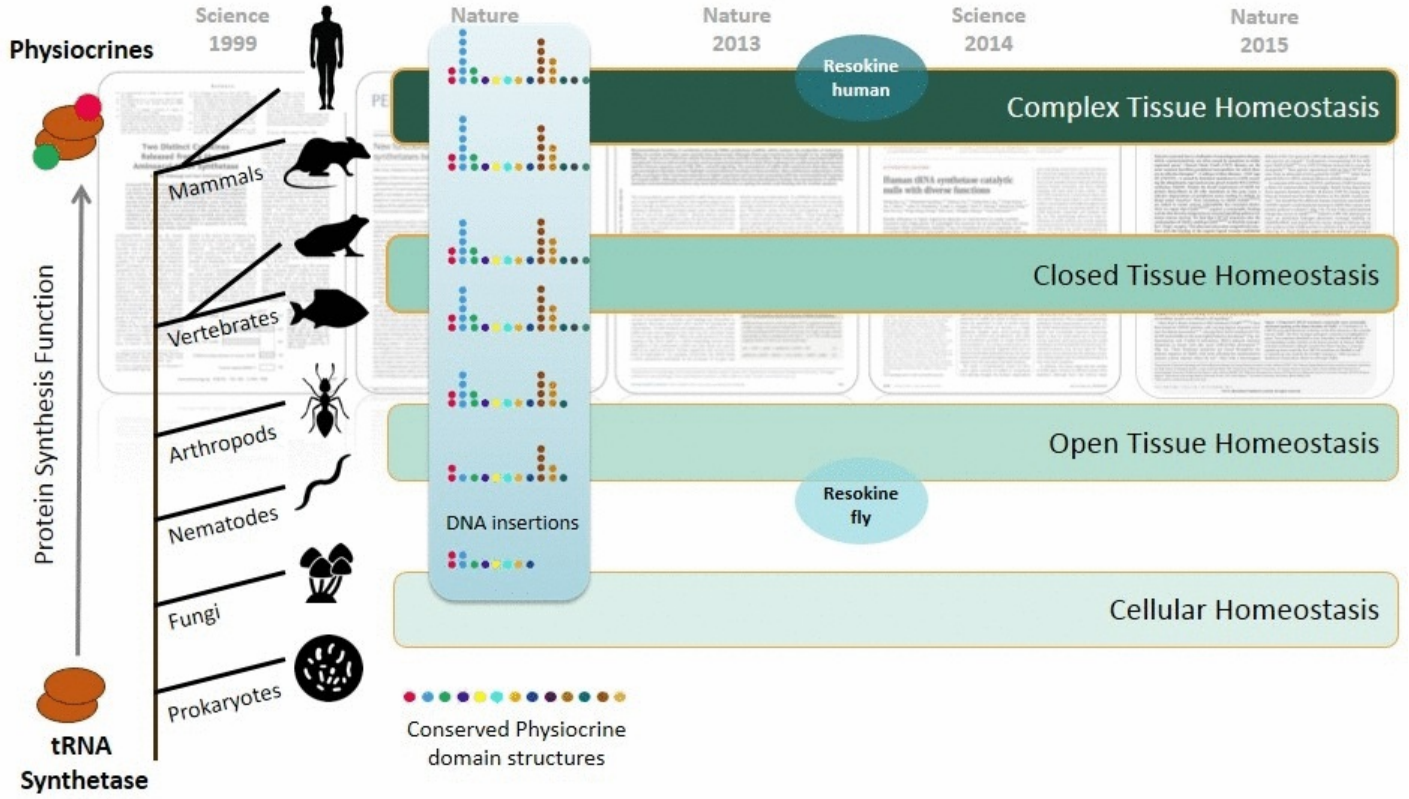
- Sanjay Shukla, MD, MS, Chief Medical Officer, aTyr Pharma

Question & Answer Session

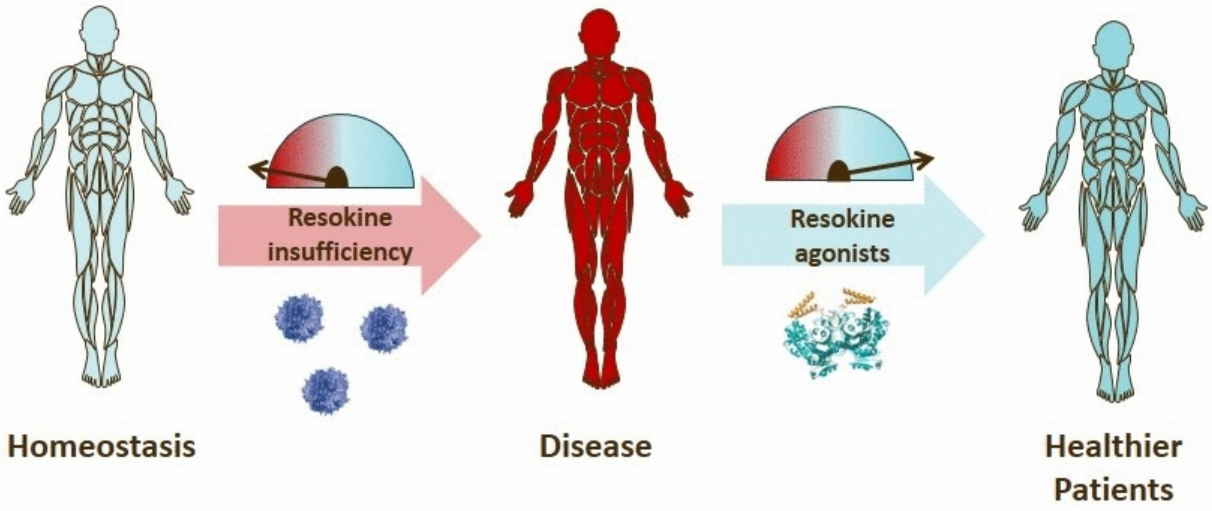

New Immunological Pathway: Resokine
Evolved from Cellular Homeostasis Genes over 400 Million Years

Resokine: Potential Key Regulator of Homeostasis

Evolved with System Complexity



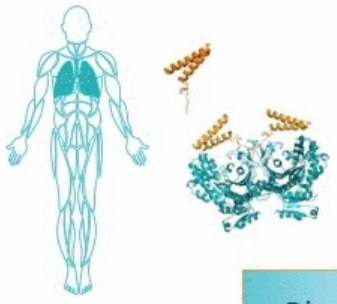
LIFE's Therapeutic Paradigm



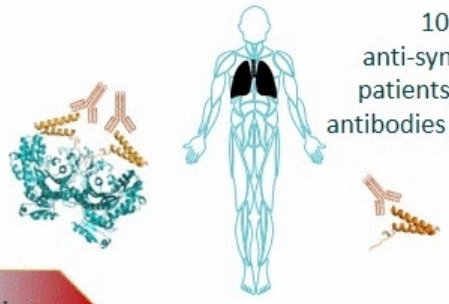
Disrupting the Resokine Pathway Promotes ILD

Evidence for Homeostatic Role of Resokine in Humans

Homeostasis

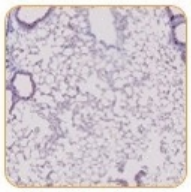


Imbalance



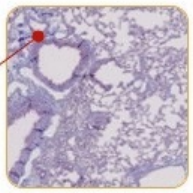
100% (18 of 18) anti-synthetase syndrome patients tested positive for antibodies for Resokine proteins

Disease antibodies



Healthy lung

↑ Immune cell Invasion / activity



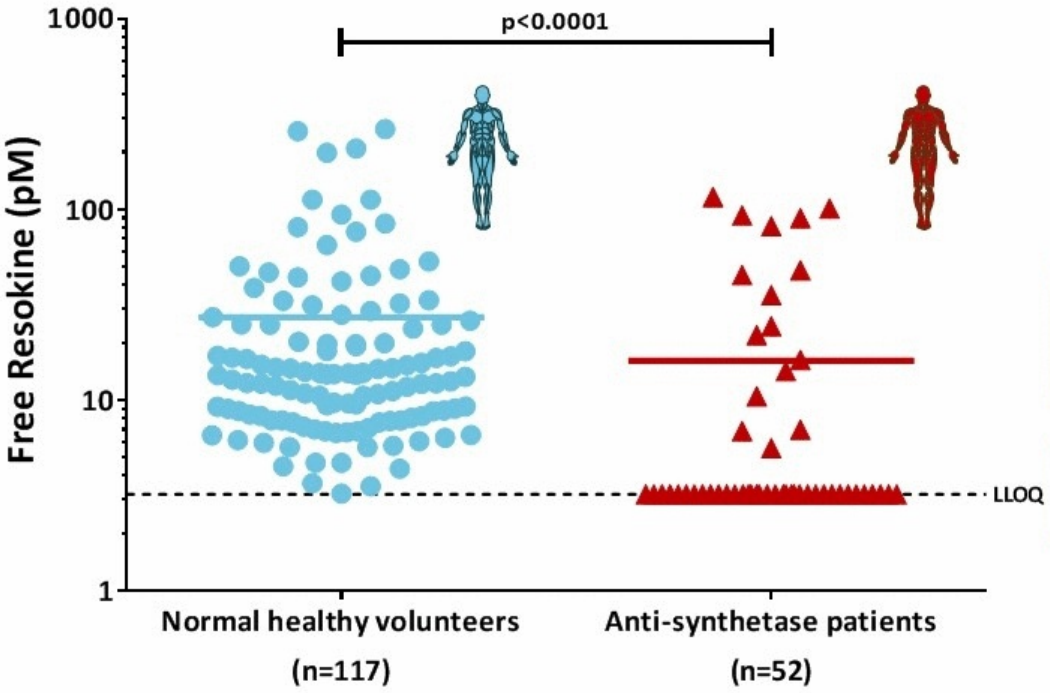
Diseased Lung

Lung Characteristics

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

BALF = bronchoalveolar lavage fluid; NSIP = non specific interstitial pneumonia; DAD = diffuse alveolar damage

Free Resokine Pathway in Anti-Synthetase Patients Diminished



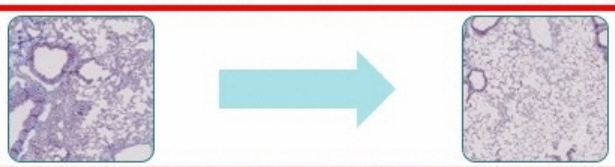
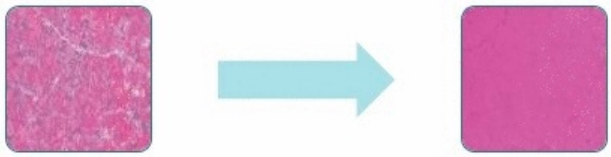
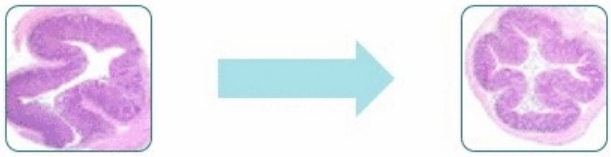
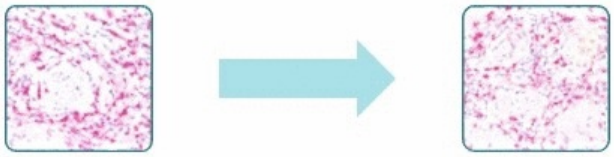
>85% of patients develop Interstitial Lung Disease (ILD)

69% at or below limit of detection

Unpublished data from aTyr and collaborator
Statistics: Mann-Whitney test

Agonists of the Resokine Pathway in Immune Driven Models

Balancing the immune response to tissue insults

Disease Model	Resokine Homeostatic Effect	Immune Targets
Lung Bleomycin Induced Lung Fibrosis		Th17/CD4
Skeletal Muscle Statin Induced Myopathy		CD4/CD8 & macrophages
Colon TNBS Induced Colitis		Th17/CD4
Skin IL23 Induced Psoriasis		Th17/CD4

In vivo administration of Resokine proteins to animal models of T cell driven disease states.
Cell type indicates type of cells involved but may not be limited to these cells.

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

***TPP** = Target Product Profile*

***ILD** = Interstitial Lung Disease; **IPF** = Idiopathic Pulmonary Fibrosis*

Overview of Interstitial Lung Disease

Steven Nathan, MD

Medical Director,

Advanced Lung Disease & Transplant Program

Inova Fairfax Hospital

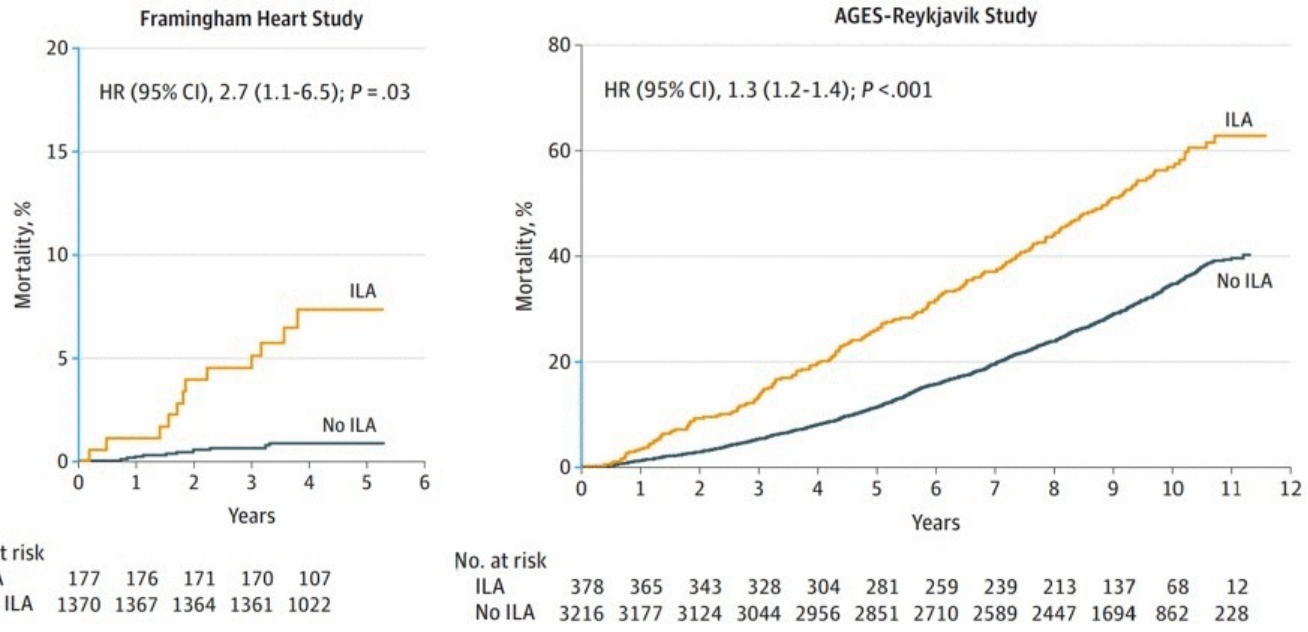
Falls Church, Virginia USA

Disclosures: Steven Nathan, MD

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

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

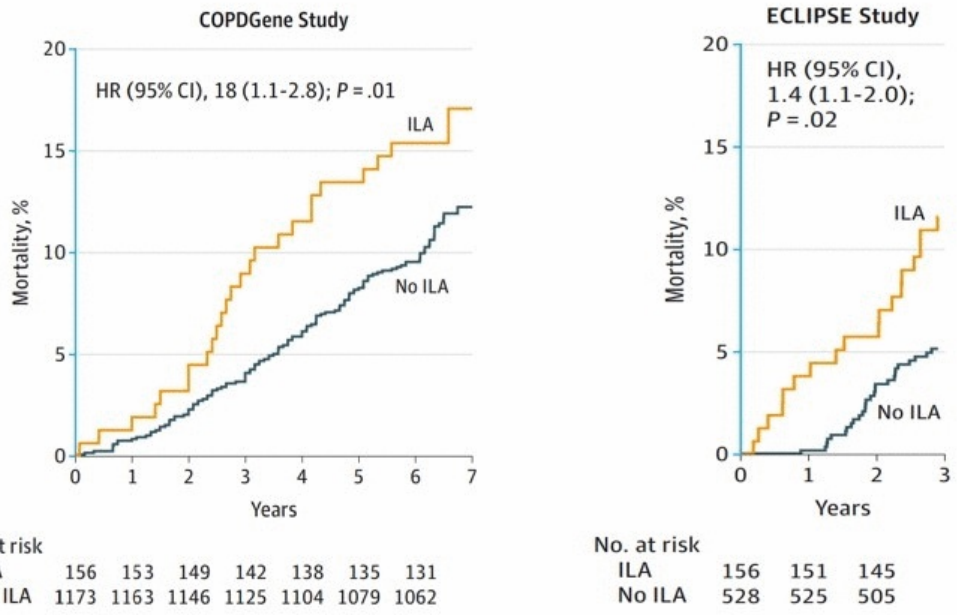
Association between Interstitial Lung Abnormalities and All-cause Mortality



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

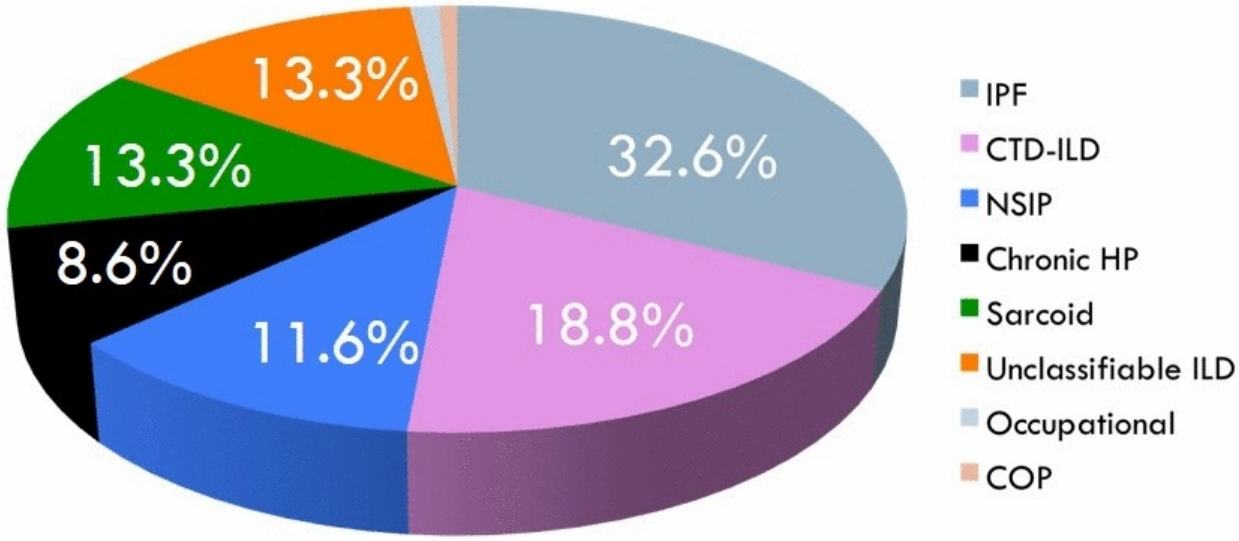
ILA	156	151	145
No ILA	528	525	505

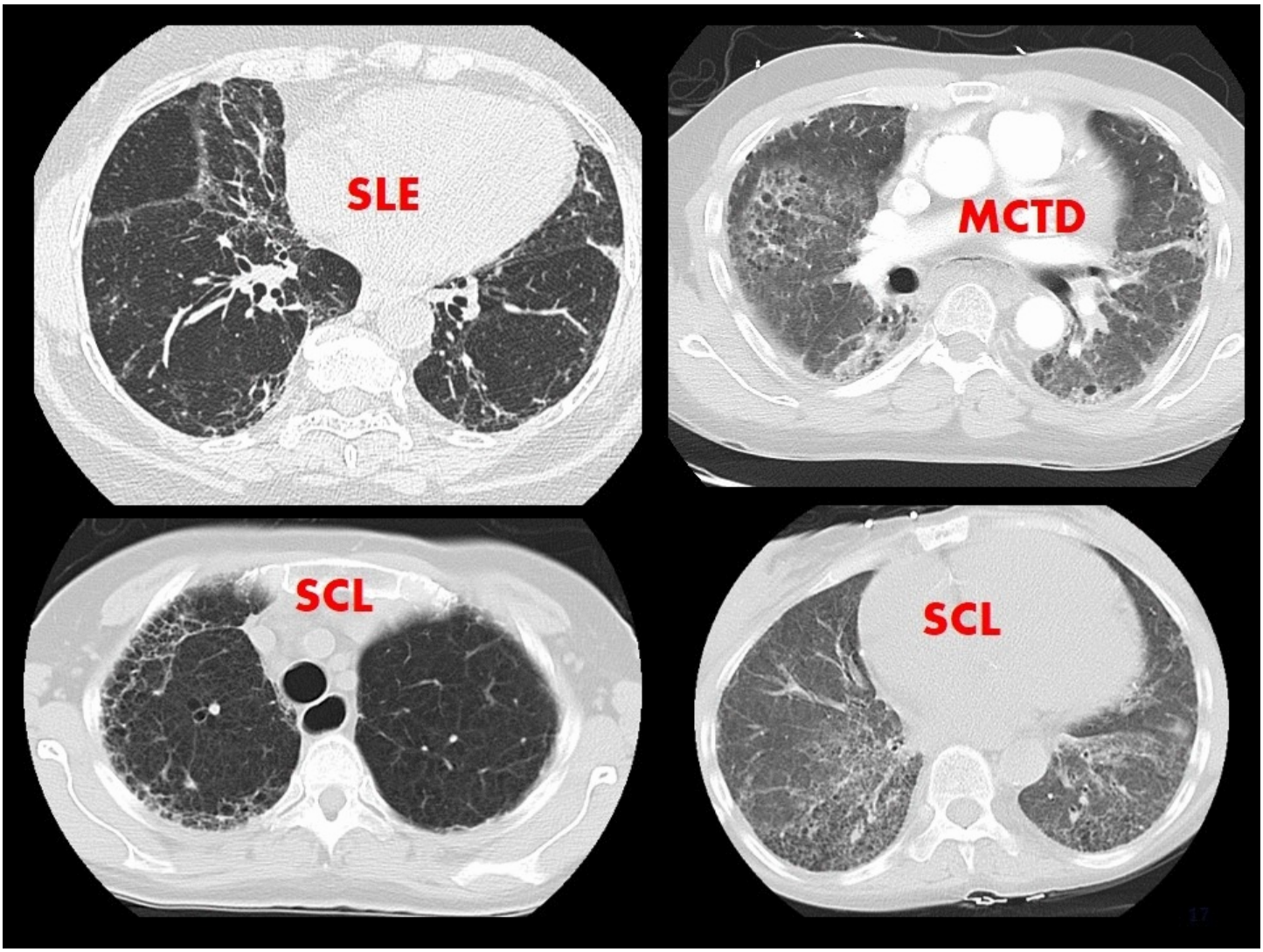
Blue segments of y-axes indicate mortality range from 0% to 20%. P values included in each panel are associated with hazard ratios (HRs [95% CIs]) from the adjusted Cox proportional hazards model including adjustments for age, sex, race, body mass index, pack-years of smoking, current or former smoking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

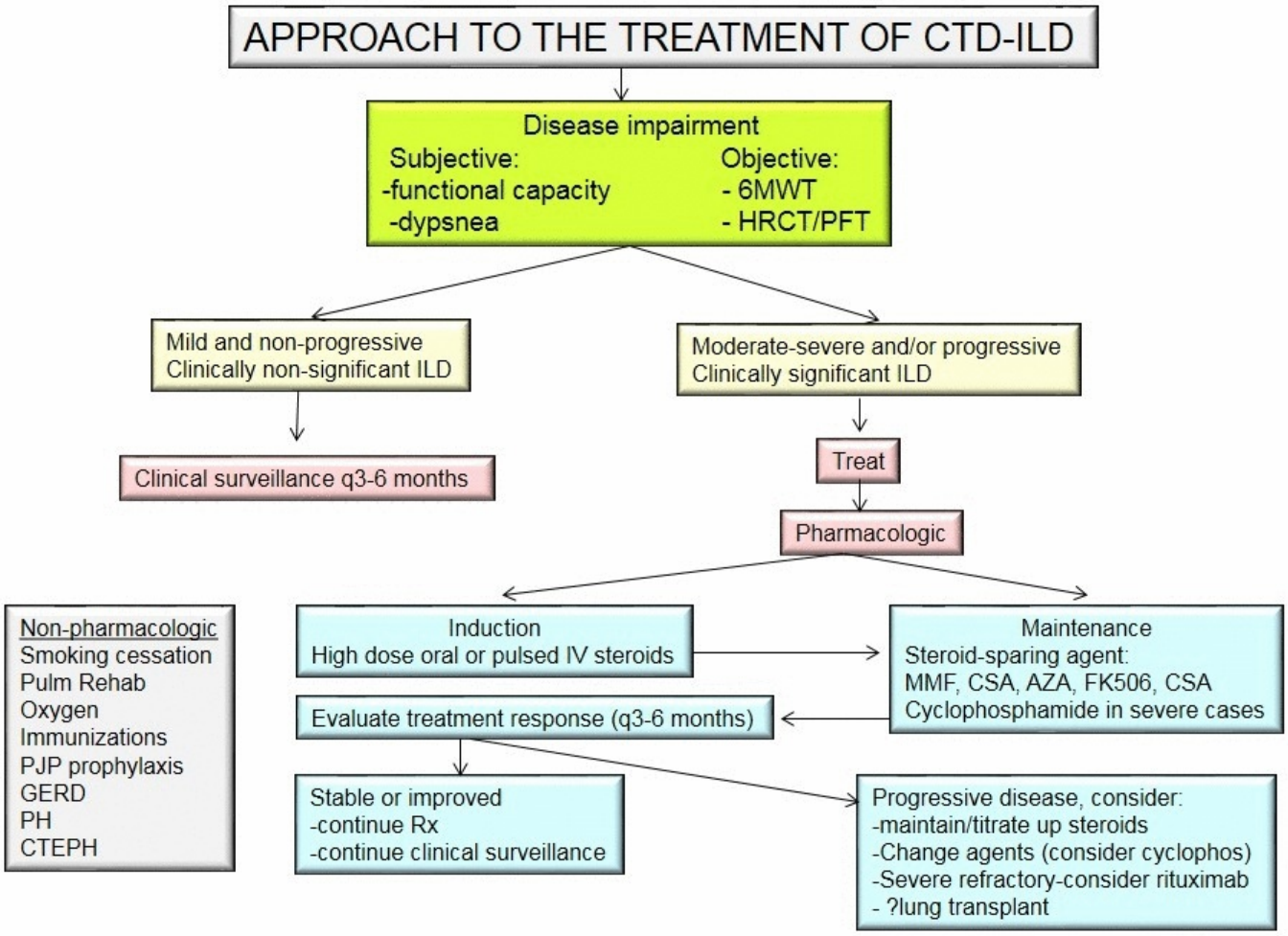
Spectrum of ILD followed by Inova ALD Program (N=657)




SLE
MCTD
SCL
SCL

Prevalence of ILD in CTD

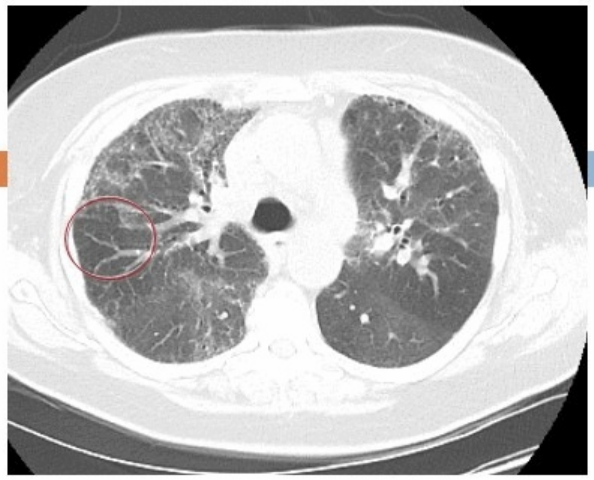
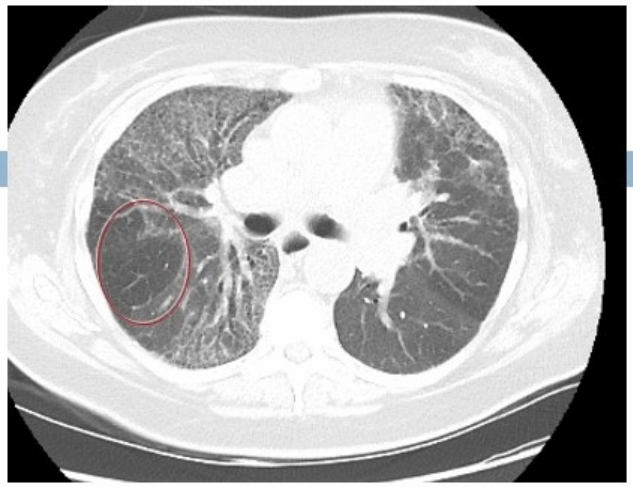
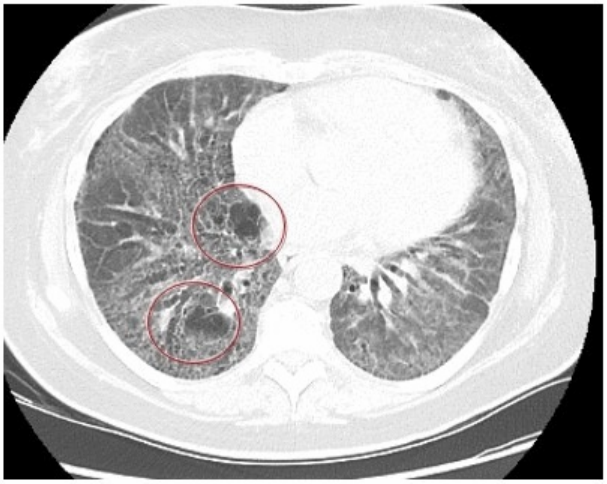
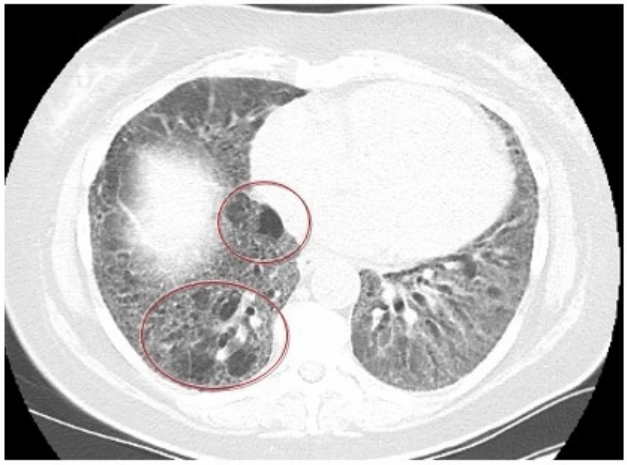
- 1,600 deaths in USA annually
  - 25% of all ILD deaths
  - 2% of respiratory deaths
- RA: 15-20%
- PM/DM: 5-20%
- SLE: 5-18%
- Scleroderma: 50-70%
- Sjogrens:5-40%



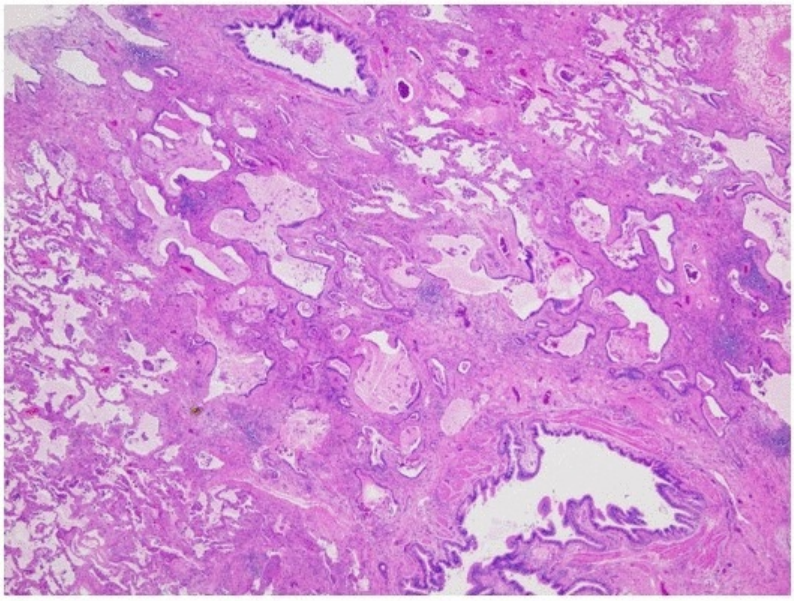
Adapted from Chartrand, Fischer. Sarc Vasc;2015:32:2-21

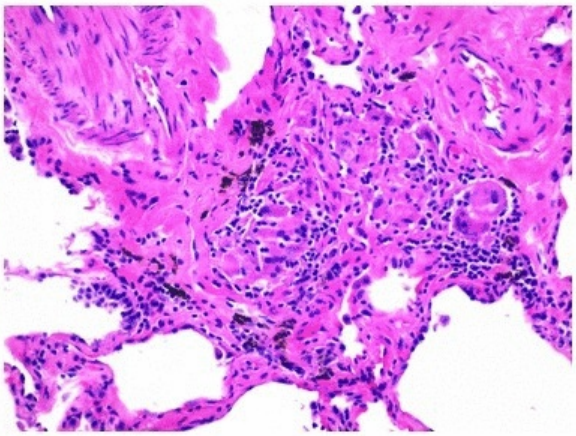
Chronic Hypersensitivity Pneumonitis

- 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

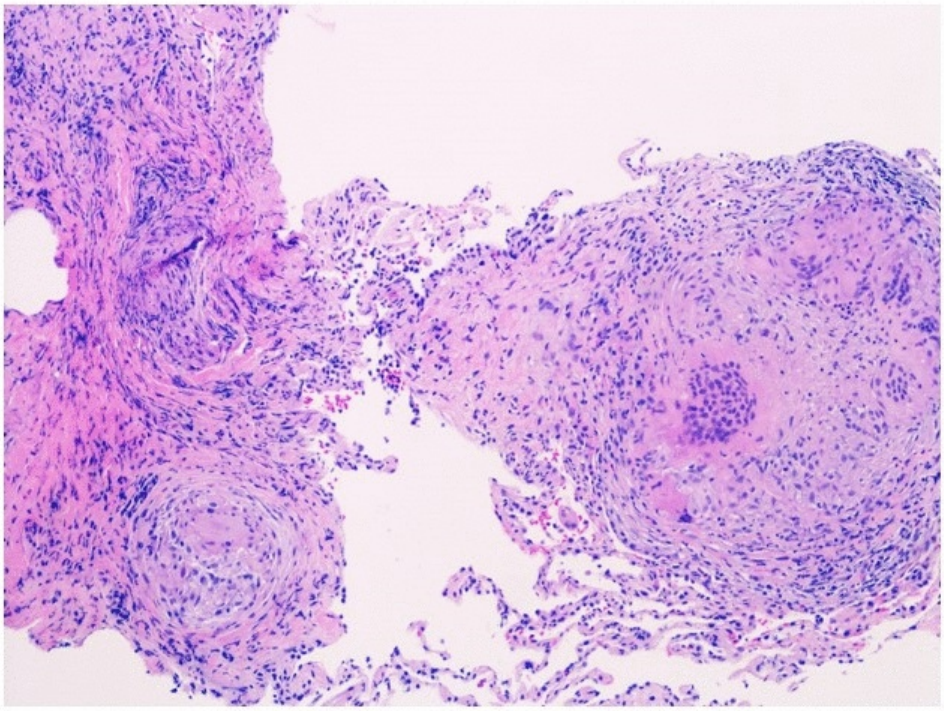


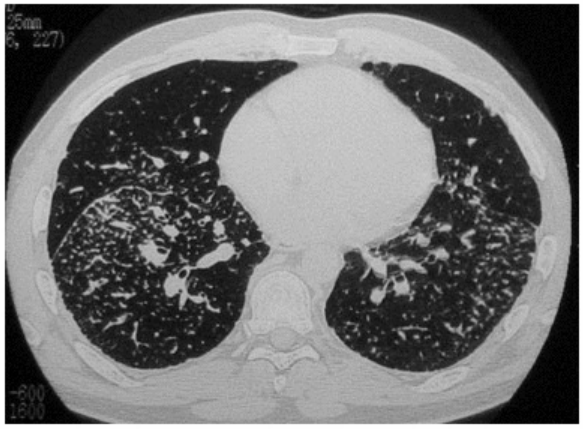


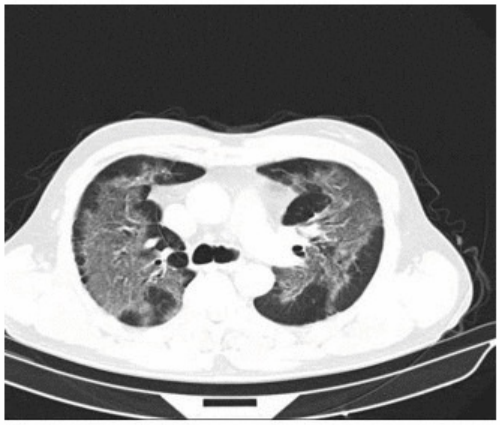
Sarcoidosis: Systemic Disease

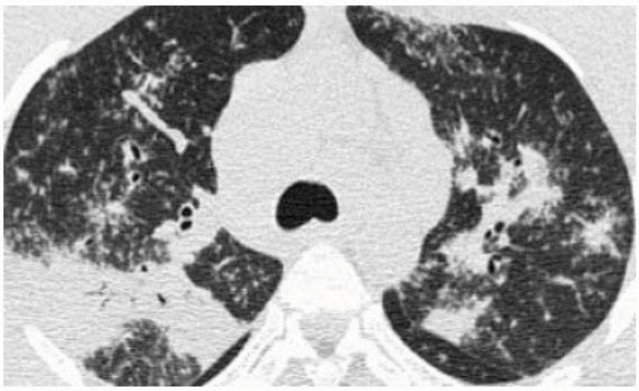
- A multisystem disease
  - Unknown etiology
  - Granulomatous disorder
  - Affects individuals world wide
  - Most often affects young adults
- Prevalence of 10-20 per 100,000 population
- Incidence is unknown
  - Varies among geographical groups
  - Lifetime incidence in blacks is 2.4%, in whites 0.85%

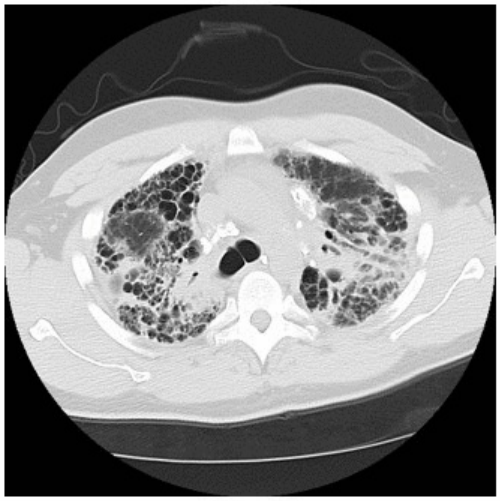
Non-Caseating Granulomas











Treatment of Sarcoidosis

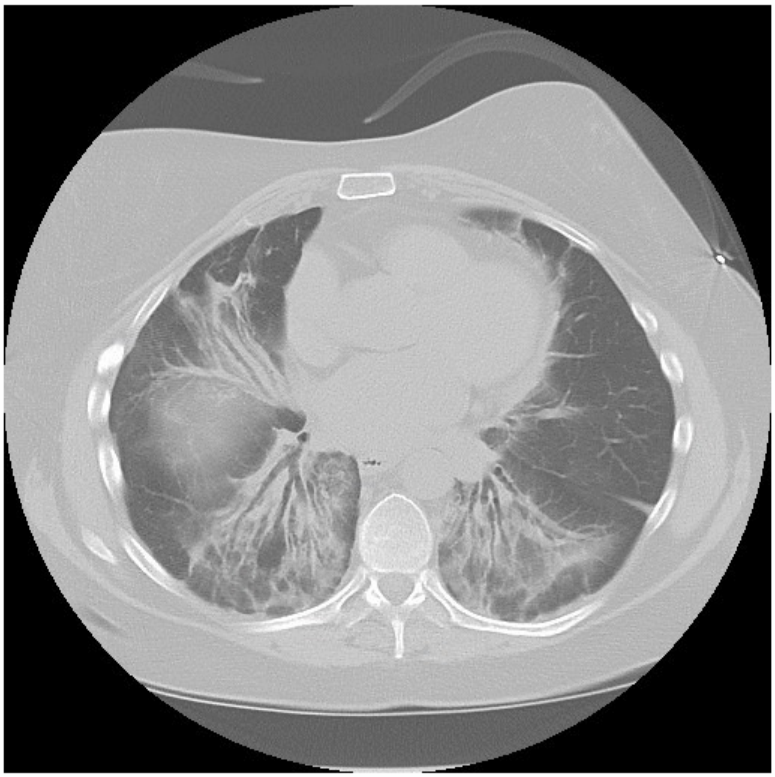
- Not all patients require therapy for sarcoidosis
  - About half never get treated
    - Pulmonary, ocular, neuro, cardiac, hypercalcemia
- Treatment strategies are different based on phase of disease
  - Acute
  - Chronic
  - Refractory
  - Steroids, methotrexate, azathioprine, mycophenolate, leflunomide,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

Revised ATS/ERS Idiopathic Interstitial Pneumonia Classification

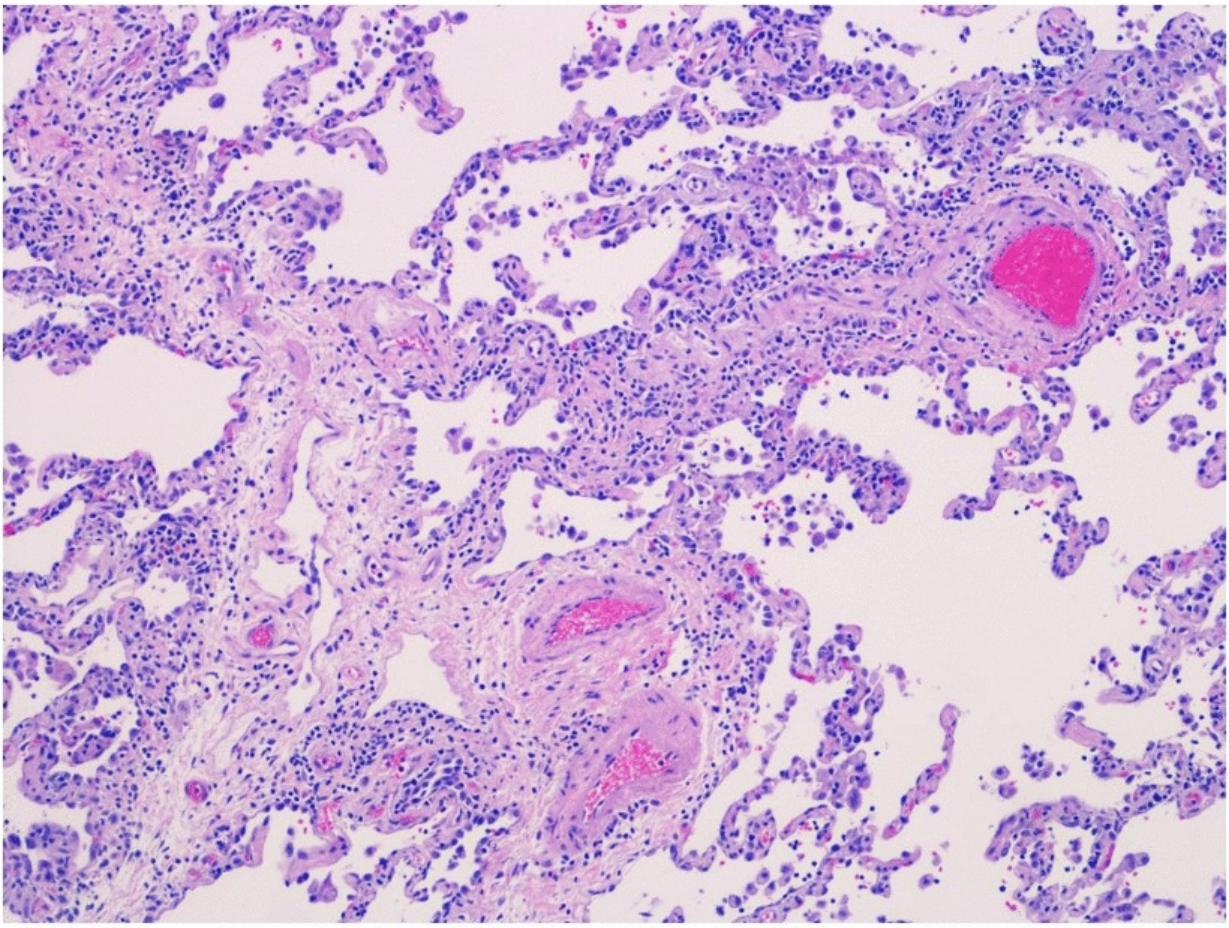
Major Idiopathic Interstitial Pneumonias
Idiopathic Pulmonary Fibrosis
Idiopathic nonspecific interstitial pneumonia
Respiratory bronchiolitis interstitial lung disease
Desquamative interstitial pneumonia
Cryptogenic organizing pneumonia
Acute interstitial pneumonia
Rare Idiopathic Interstitial Pneumonias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

Am J Respir Crit Care Med
2013;188:733-748

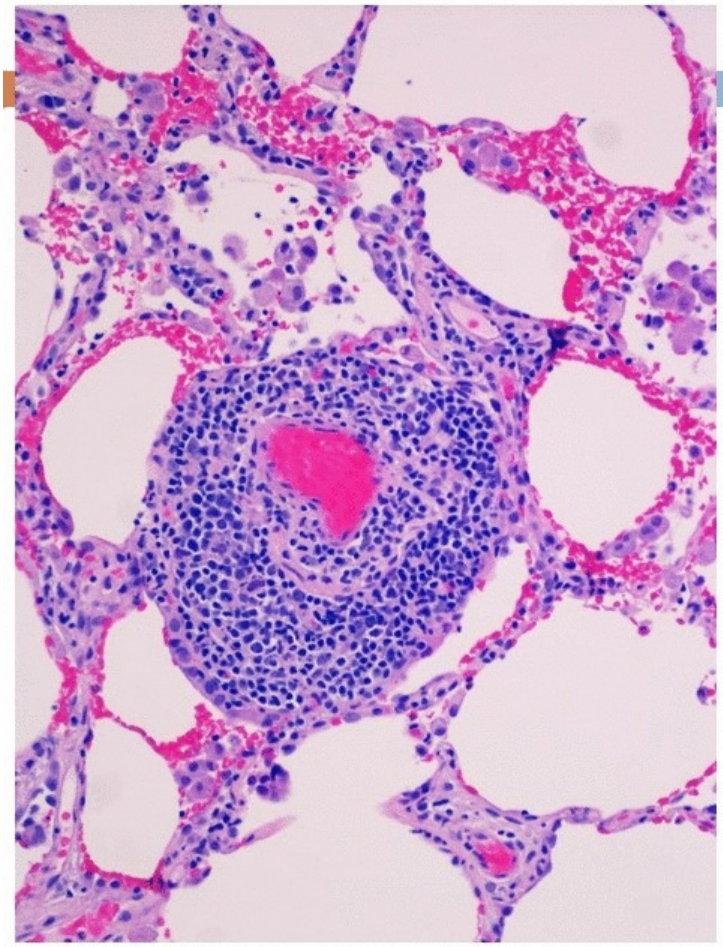
NSIP

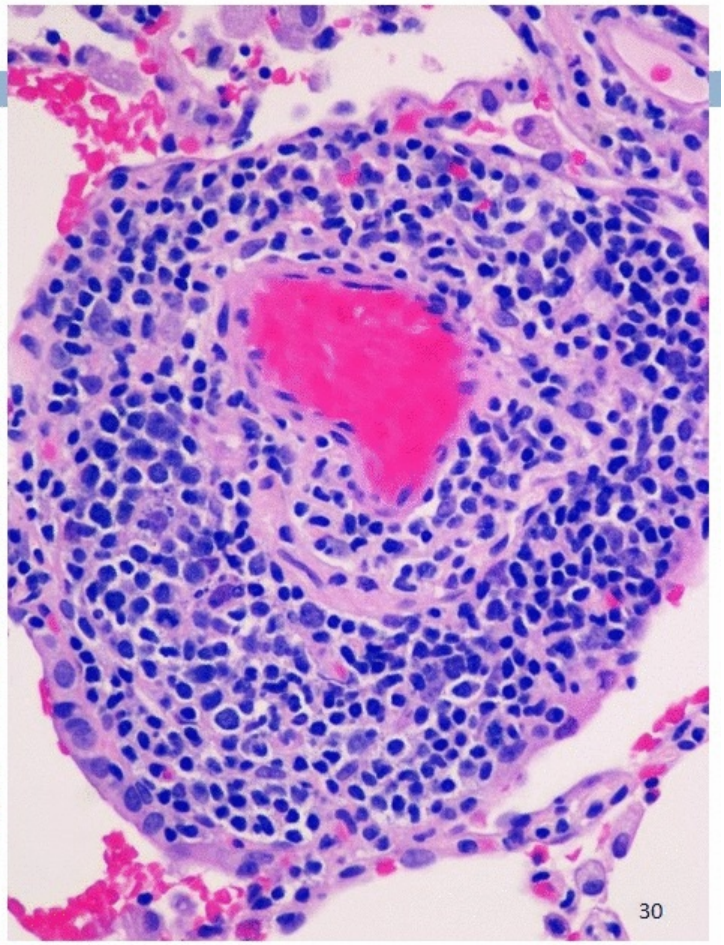


RML – adjacent mild cellular IP



RLL – venulitis



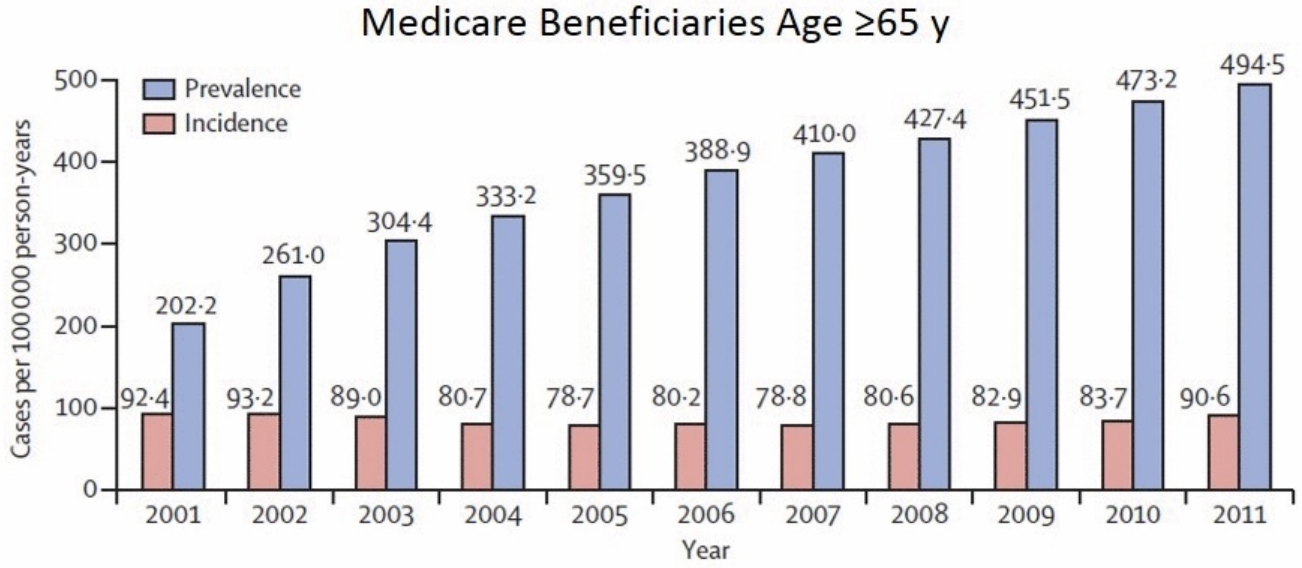


Current Definition of IPF

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

ATS/ERS/JRS/ALAT consensus statement *Am J Respir Crit Care Med.* 2011;183:788-824

Increasing Prevalence of IPF



Factors associated with lower survival

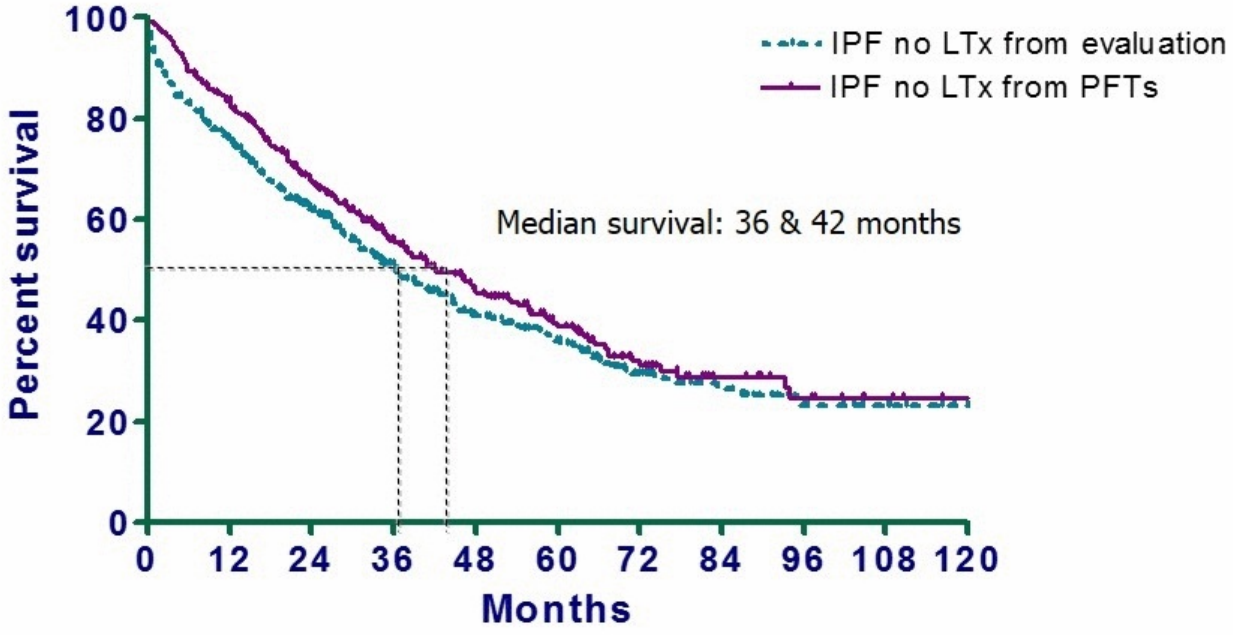
- Age, index year, male gender

Median survival = 3.8 y

1. Raghu G et al. *Lancet Respir Med*. 2014;2:566-572

IPF: Survival at the Turn of the Century

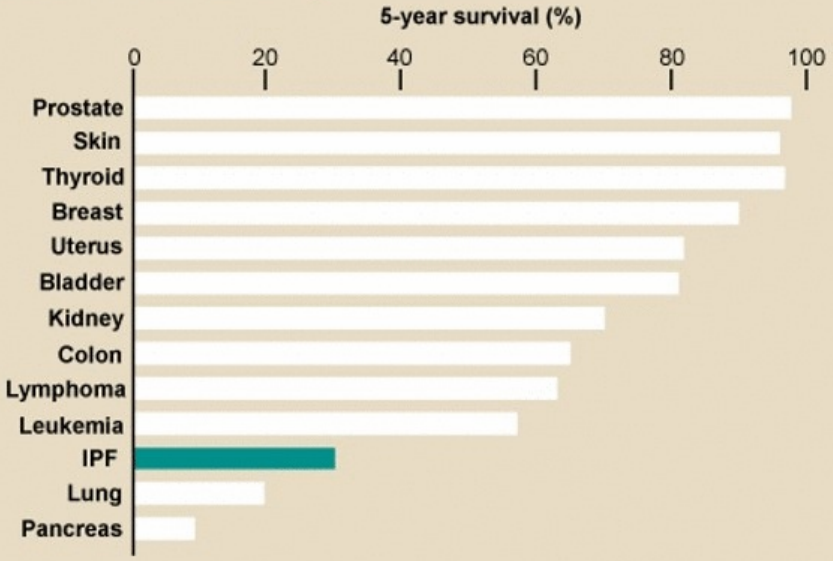
2000-2009 (N=521)



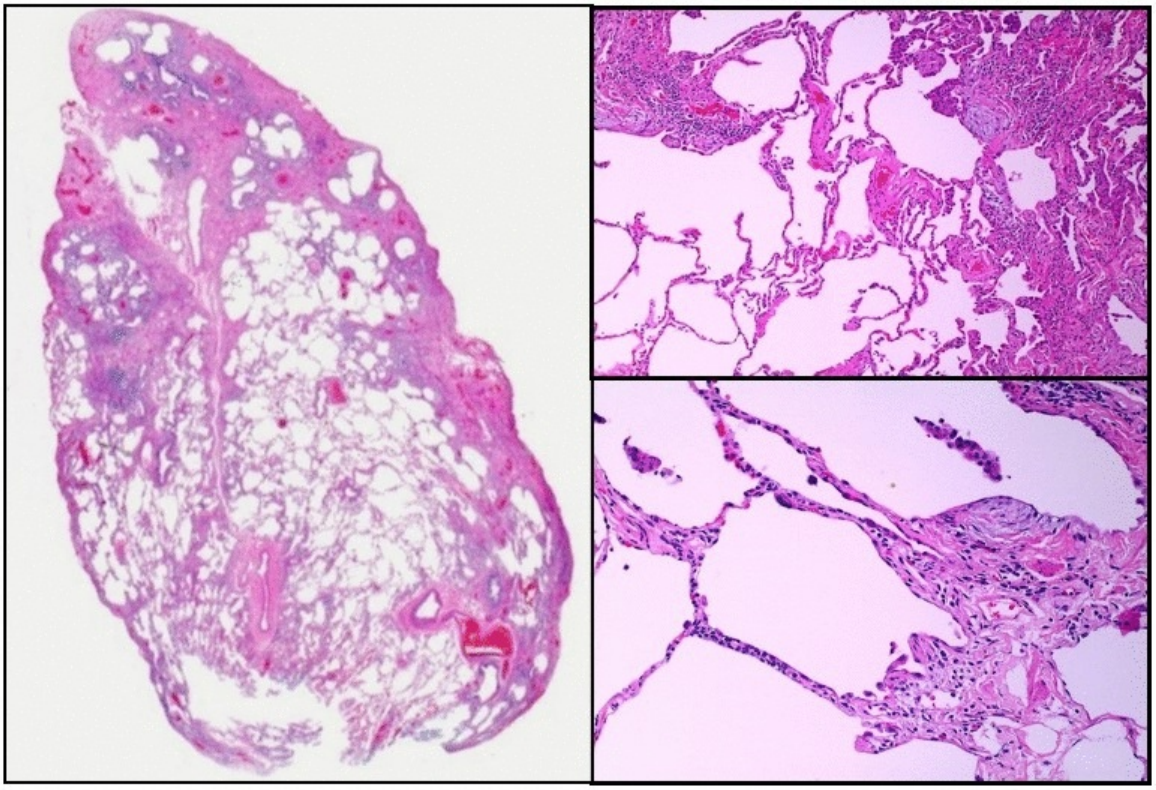
Chest 2011;140:221-229

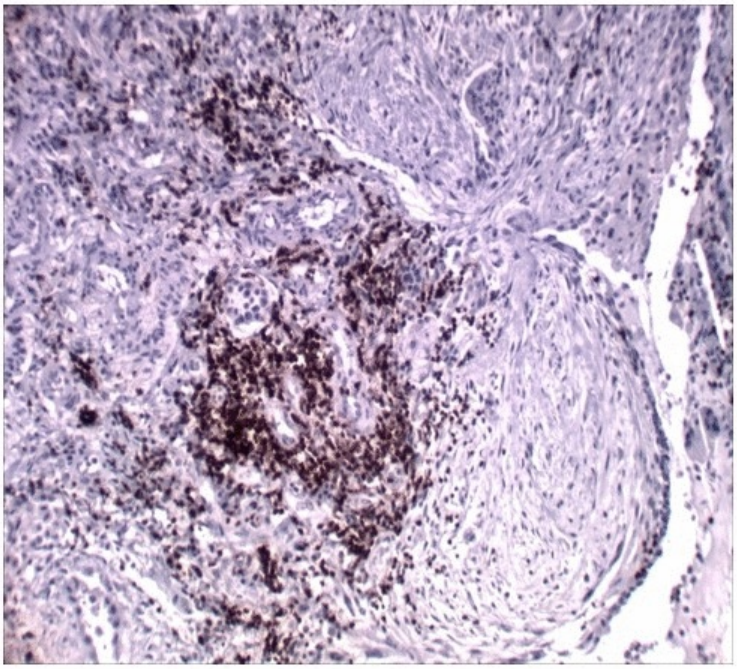
Mortality Rate High in IPF

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



Pathology: UIP Pattern





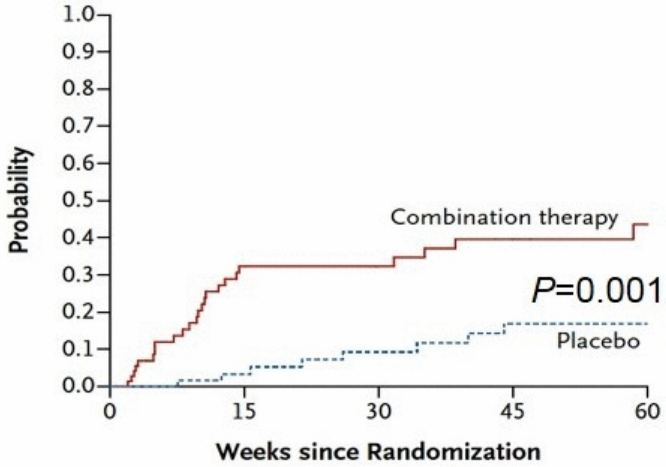
T-cells in IPF Lungs. Immunohistochemical staining shows that abnormal $CD3^+$ T-cell infiltrates (black cells near arrow) in lungs of IPF patients with usual interstitial pneumonia are distributed heterogeneously, and are often especially prominent in proximity to fibroproliferative foci (star).

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

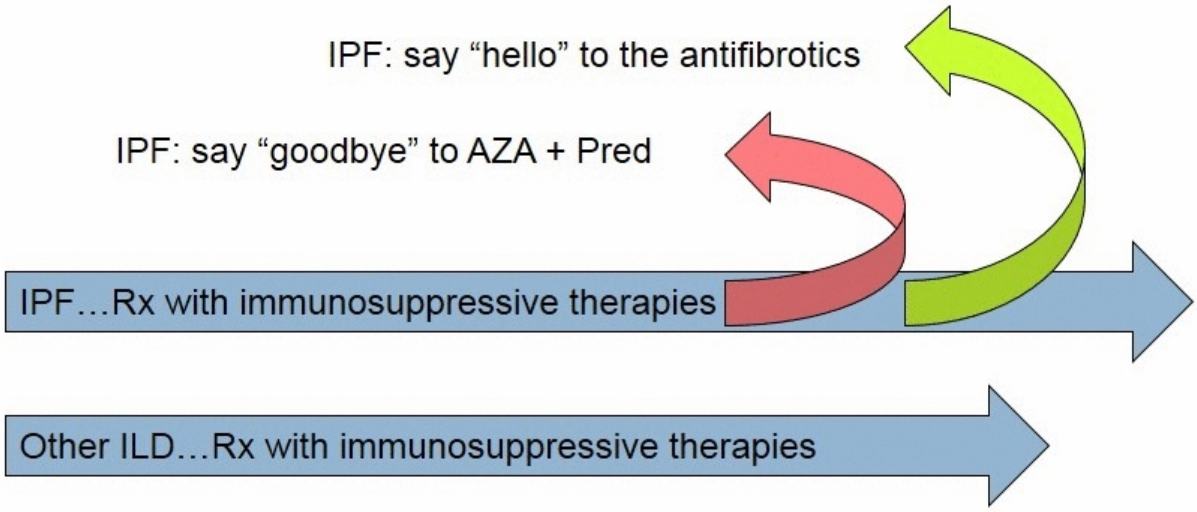


No. at Risk					
Combination therapy	77	40	29	23	10
Placebo	78	55	42	26	16

N Engl J Med 2012;366:1968-77

SEISMIC TREATMENT PARADIGM SHIFT

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



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

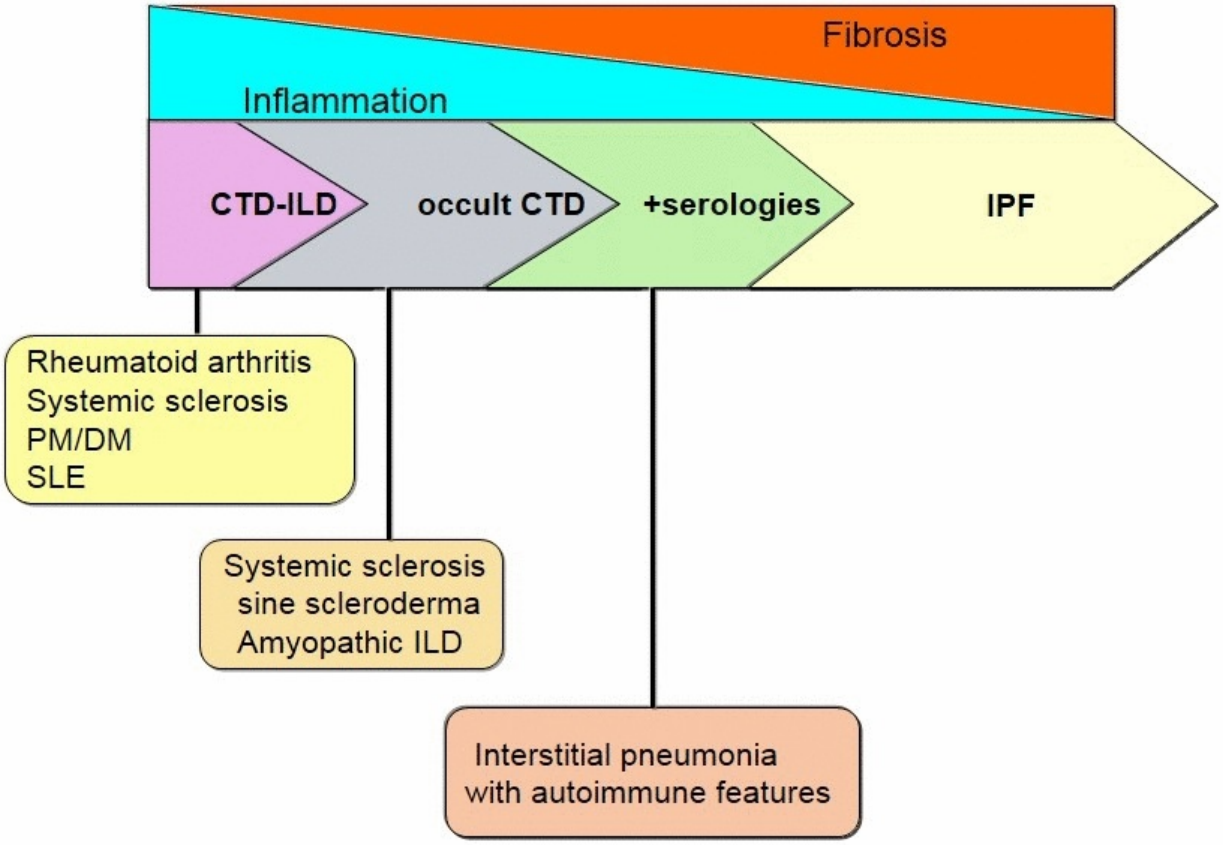
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 29, 2014 VOL. 370 NO. 22

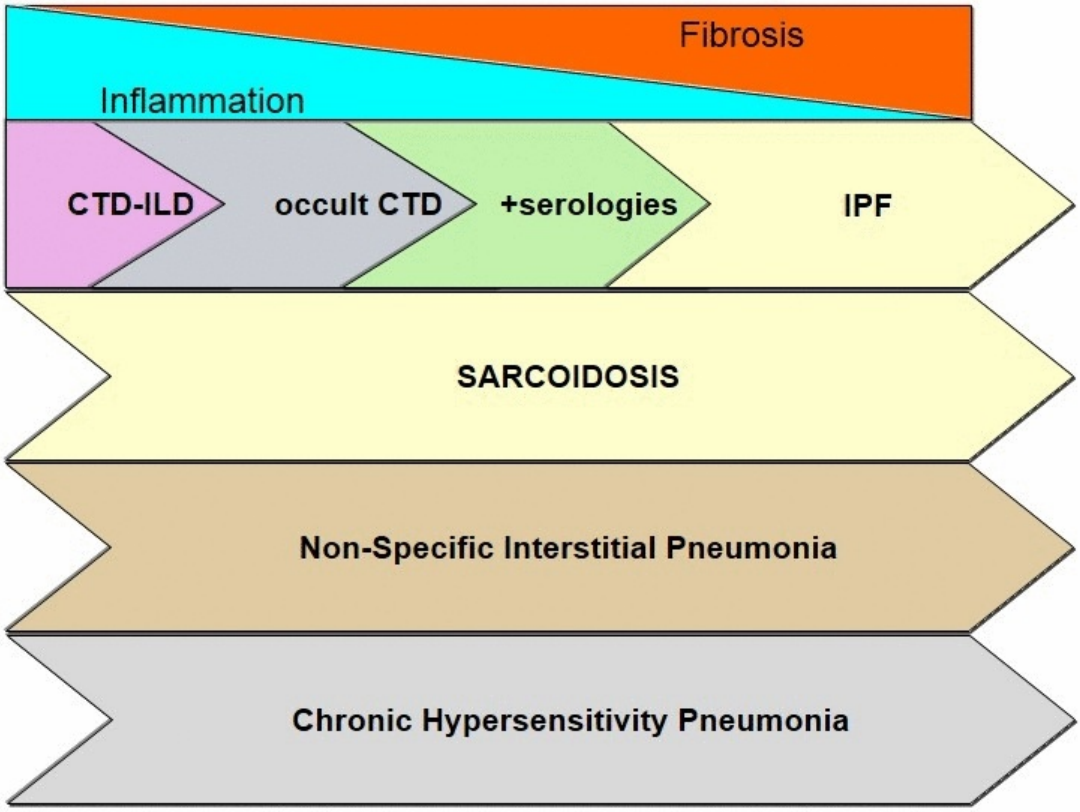
Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

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.

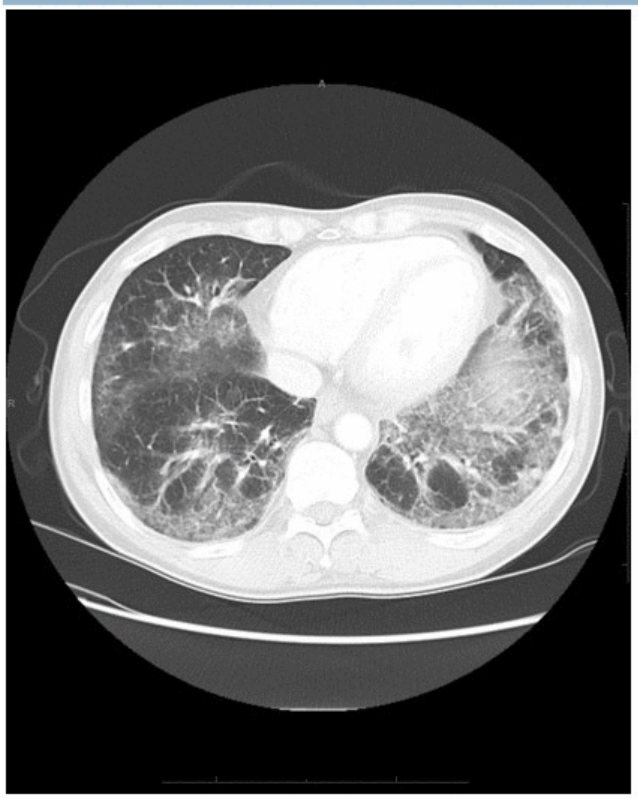
INTERSTITIAL LUNG DISEASE: A SPECTRUM

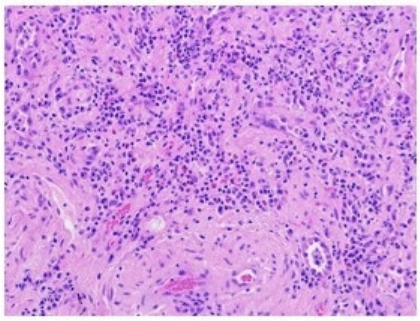


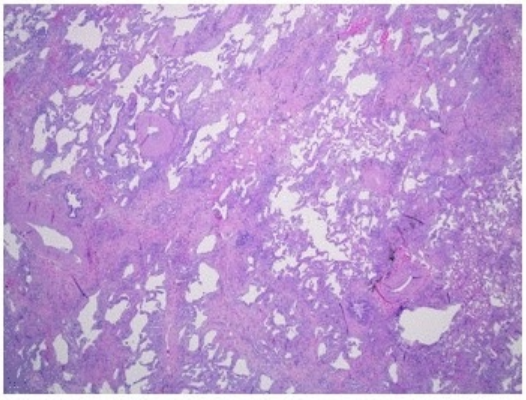
INTERSTITIAL LUNG DISEASE: A SPECTRUM

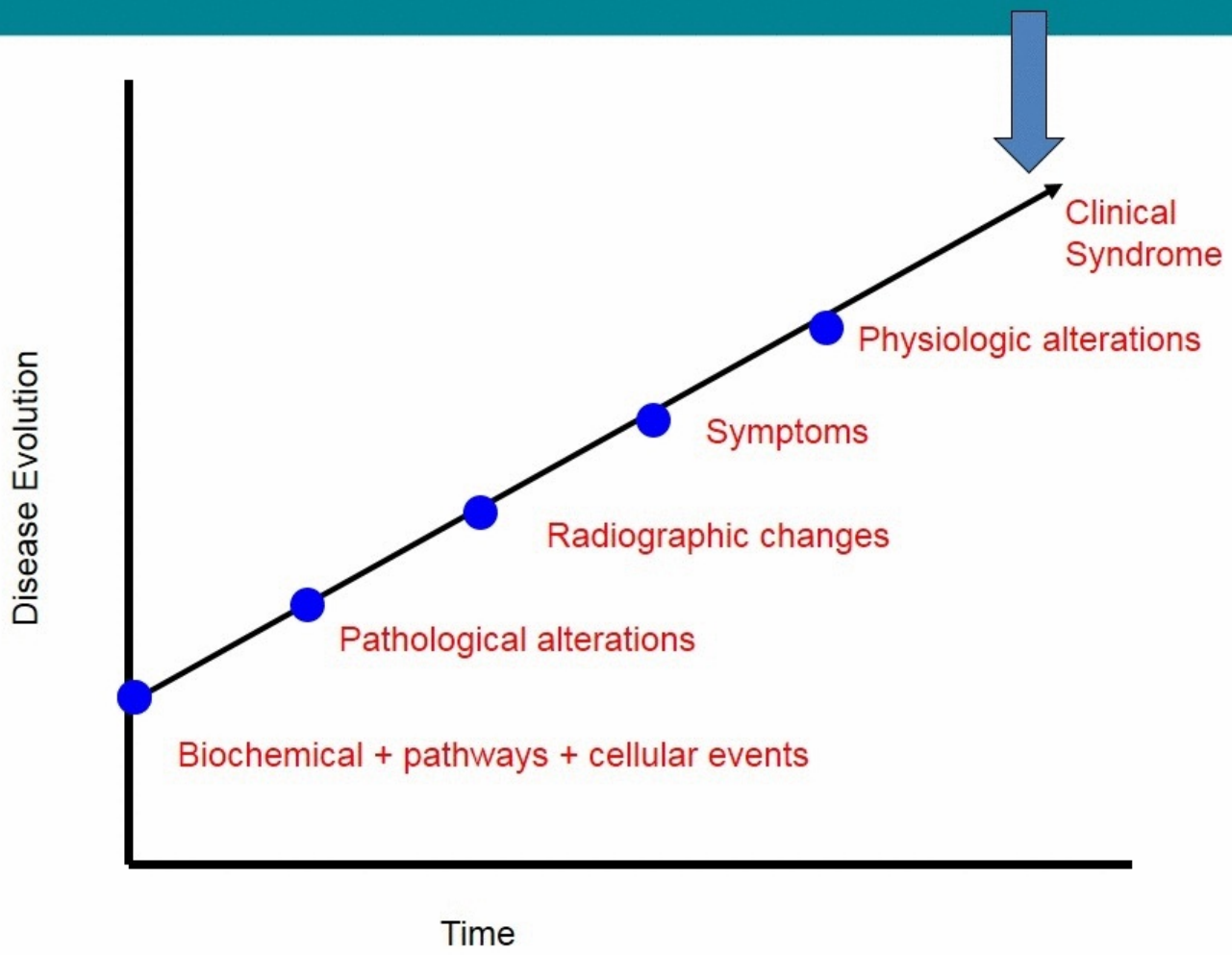


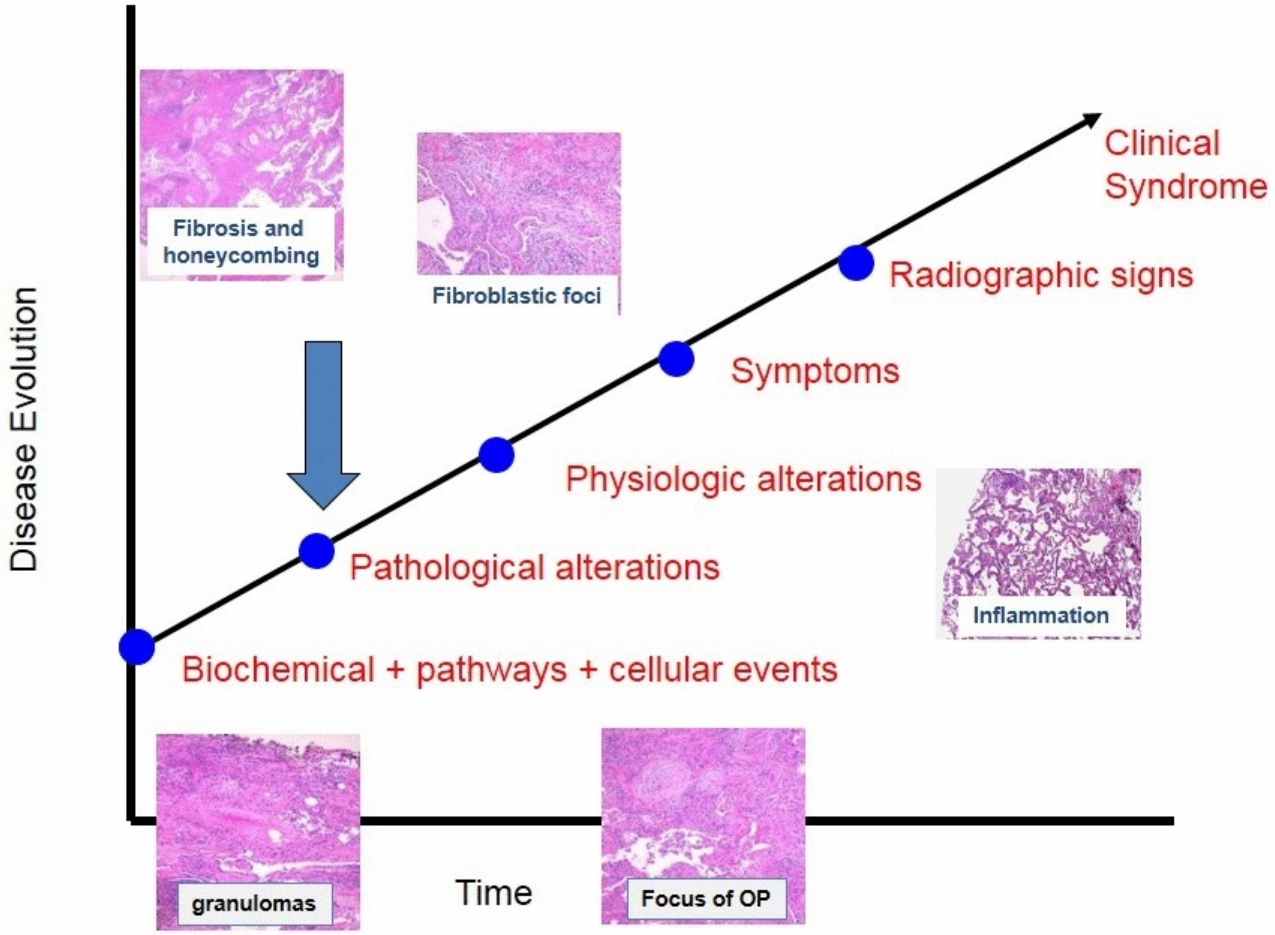
Same Case with Differing Pathology



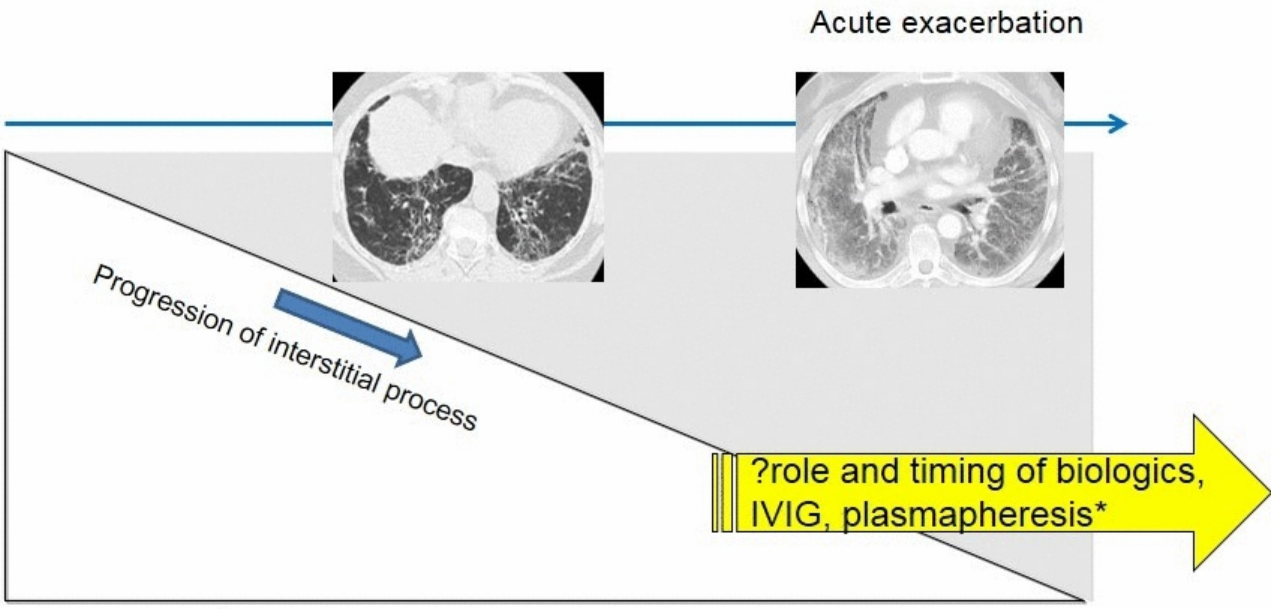




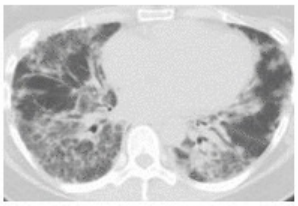

Clinical
Syndrome
Physiologic alterations
Symptoms
Radiographic changes
Pathological alterations
Biochemical + pathways + cellular events
Disease Evolution
Time


Disease Evolution
Fibrosis and honeycombing
Fibroblastic foci
Clinical Syndrome
Radiographic signs
Symptoms
Physiologic alterations
Pathological alterations
Inflammation
Biochemical + pathways + cellular events
granulomas
Time
Focus of OP

CTD-ILD: conceptual framework for future therapeutic approach



Therapy ImmunoRx

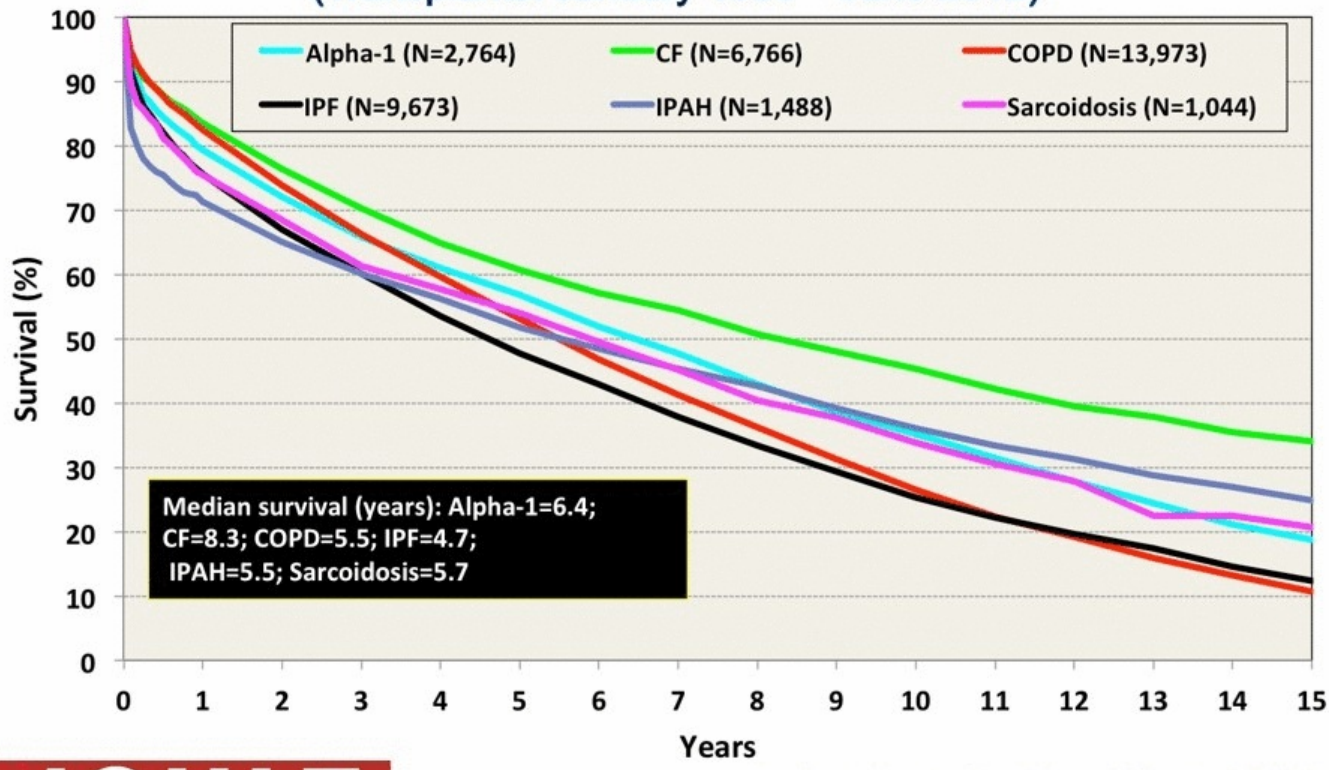


?antifibrotic*

*not recommended, await RCT evidence

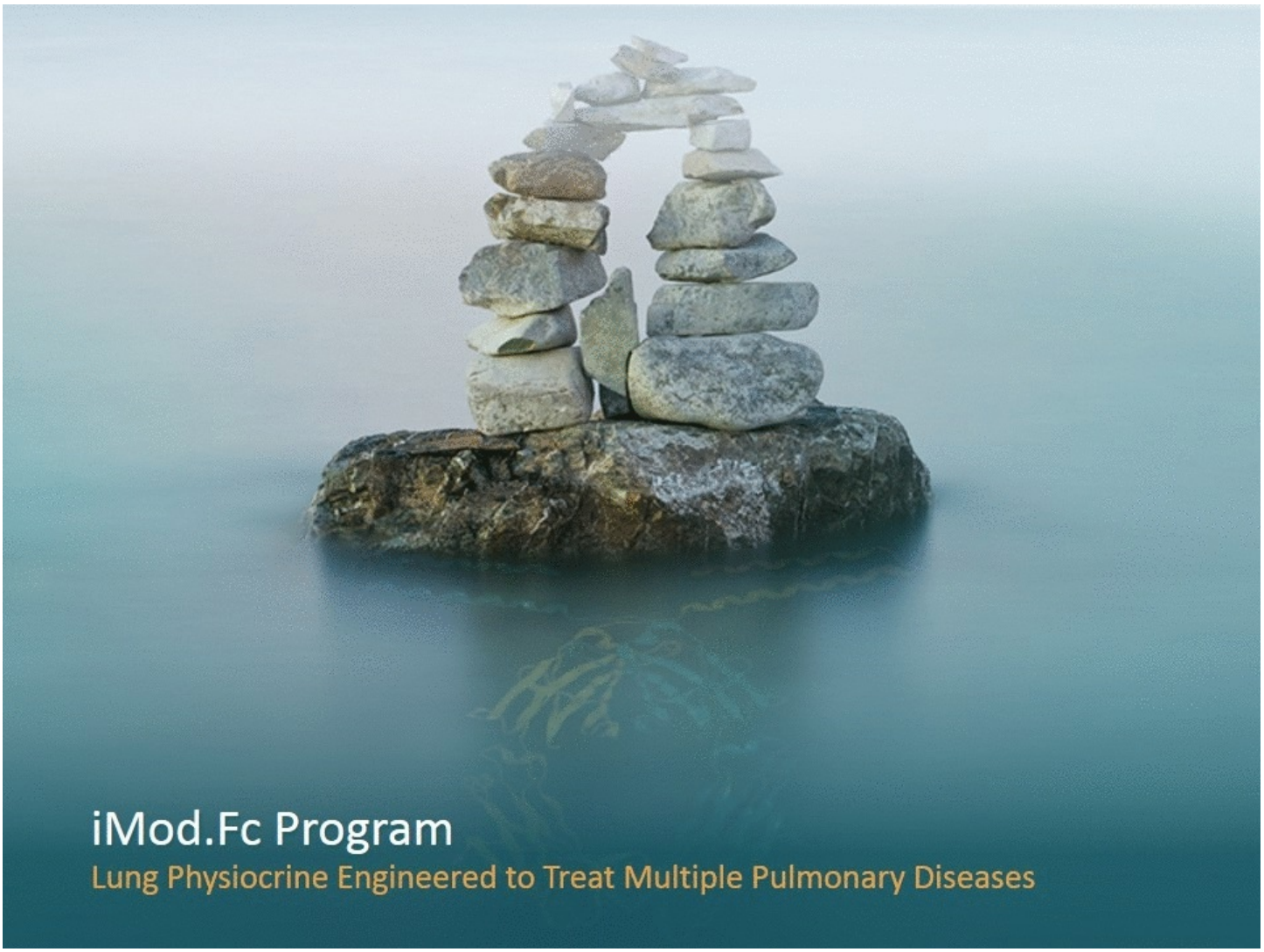
?PAH therapy *

Adult Lung Transplants
Kaplan-Meier Survival by Diagnosis
(Transplants: January 1990 – June 2012)

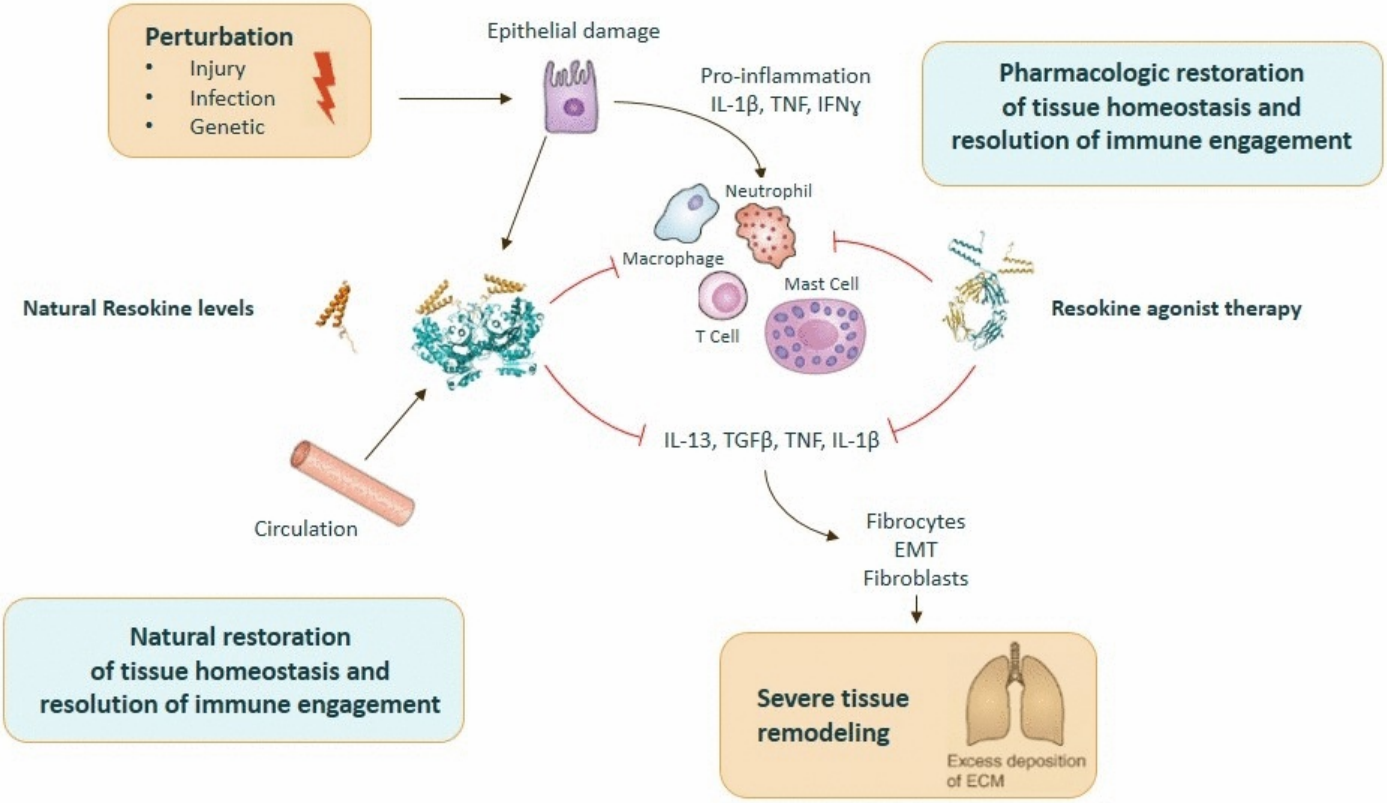


ISHLT • INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION

http://www.ishlt.org/registries/slides.asp?slides=heartLungRegistry
Accessed 9/15/2015

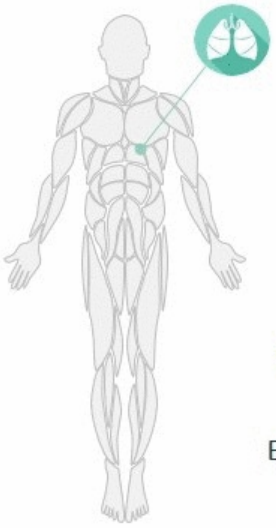

iMod.Fc Program
Lung Physiocrine Engineered to Treat Multiple Pulmonary Diseases

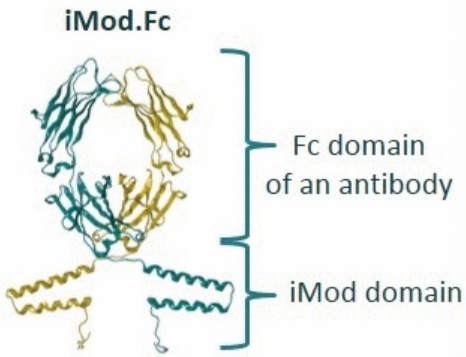
Resokine Promotes Lung Homeostasis



iMod.Fc Overview

Opportunity for Lung Patients





Engineered Physiocrine

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

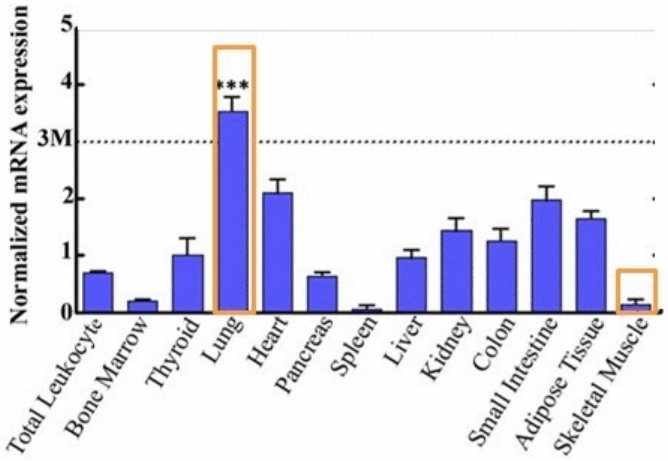
Fc domain: increased exposure to potentially enable **once-monthly dosing in humans**

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



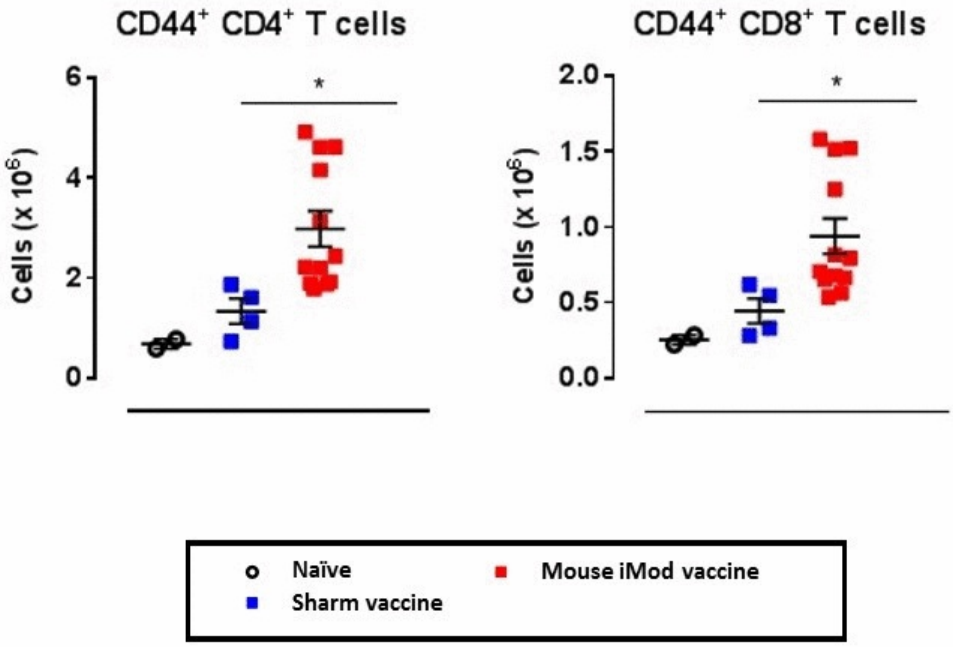
Splice variant for the **iMod domain** is relatively more expressed in **lung** than other tissues

Zhou et al. The Journal of Biological Chemistry 2014

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

Rodent functional knockout inducing idiopathic pulmonary disease using Bleomycin

T cell Invasion



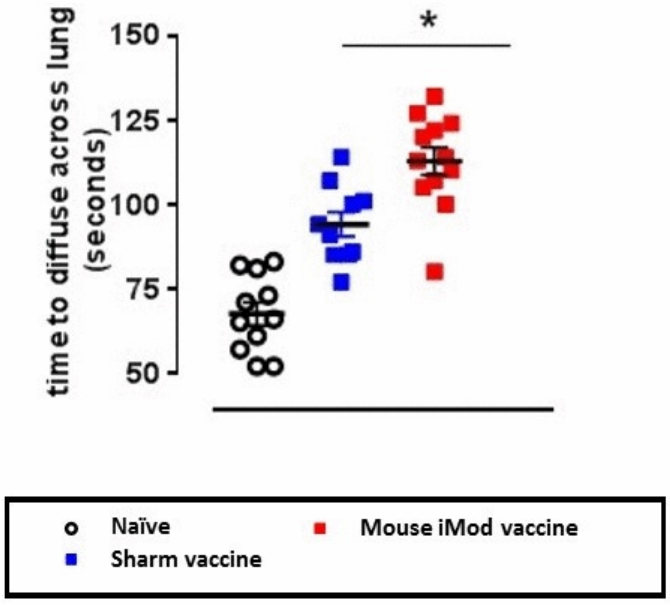
aTyr Pharma NASDAQ: LIFE

** p < .05*

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

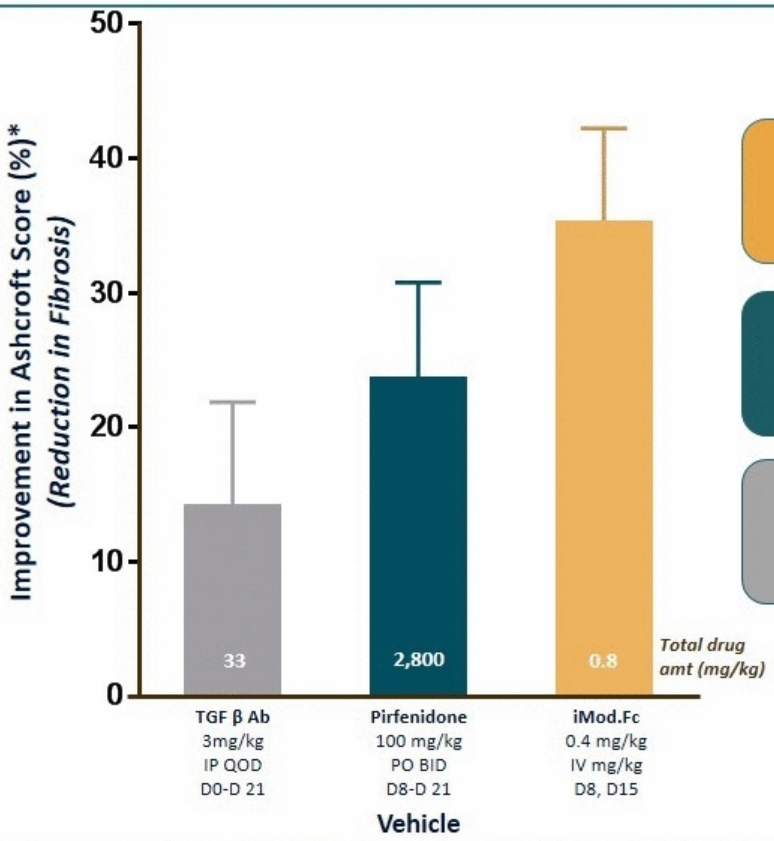


aTyr Pharma NASDAQ: LIFE

* $p < .05$

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 TGFβ Ab** doses

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**The Ashcroft scale for the evaluation of bleomycin-induced lung fibrosis is the analysis of stained histological samples by visual assessment*

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?