

Pulmonary Fibrosis and Inflammation

PD Dr. med. Manuela Funke-Chambour

Deputy chief physician

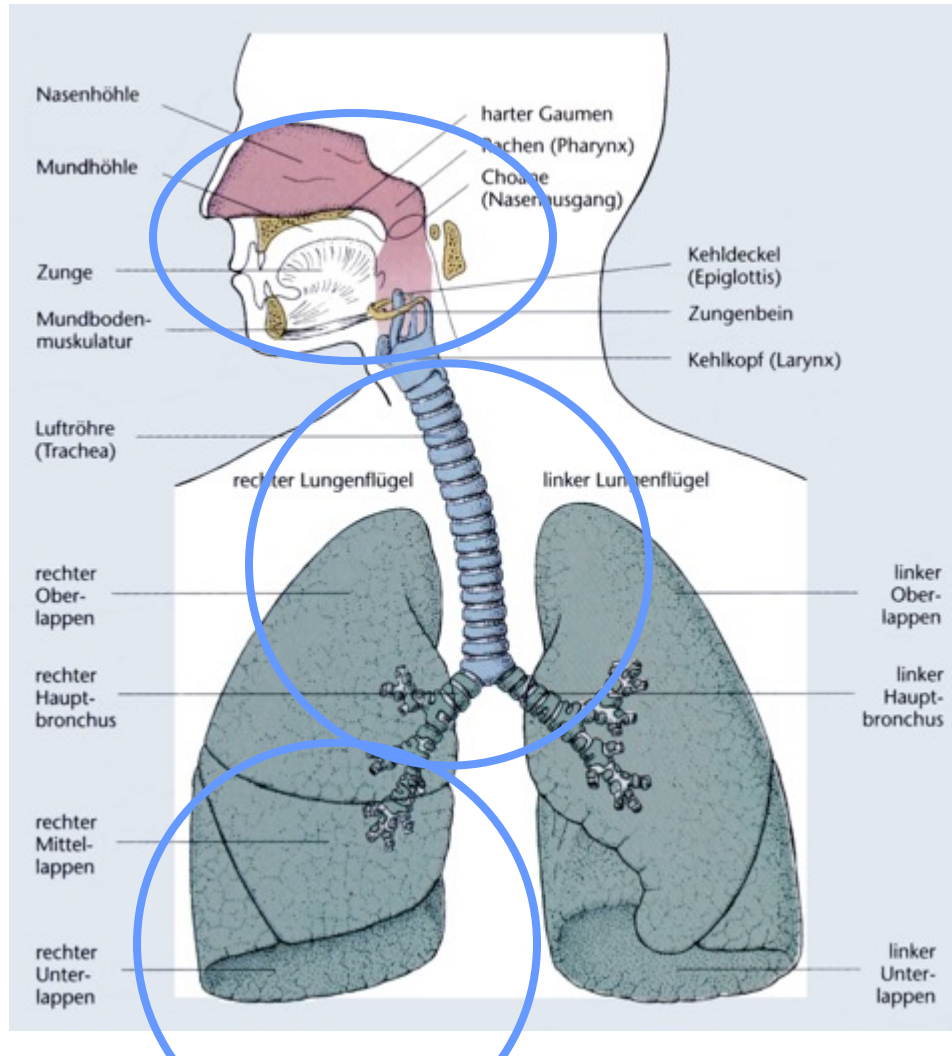
University Hospital for Pulmonology, Inselspital Berne

Pulmonary research laboratory, DBMR

Overview

1. Overview lung and lung parenchyma
2. Pulmonary Fibrosis
3. Acute exacerbation
4. Treatment options
1. Conclusion

The healthy lung



Nose, Pharynx:

Warming, humidification

Trachea, Bronchi:

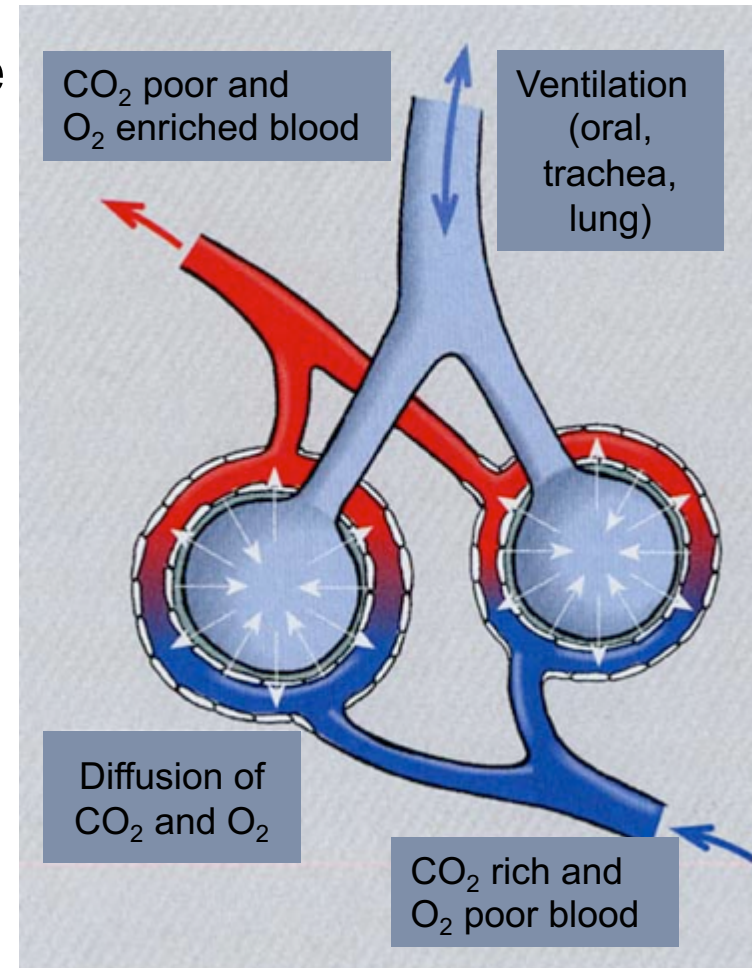
Transportation,
Immunological functions

Alveoli:

Gas exchange
Immunological functions

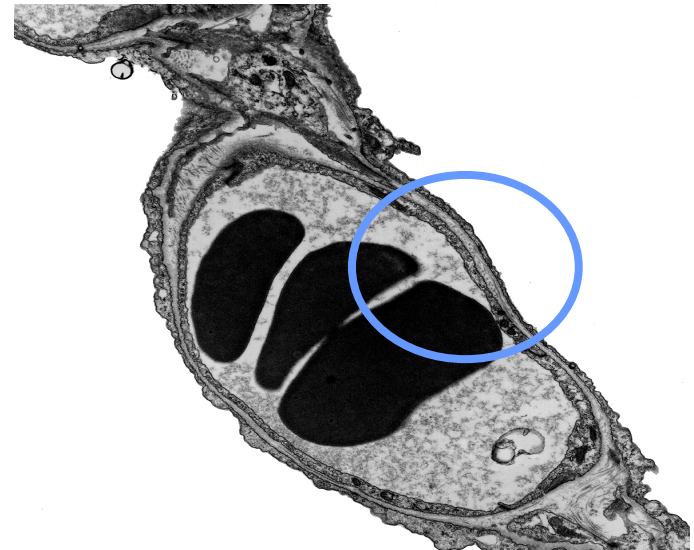
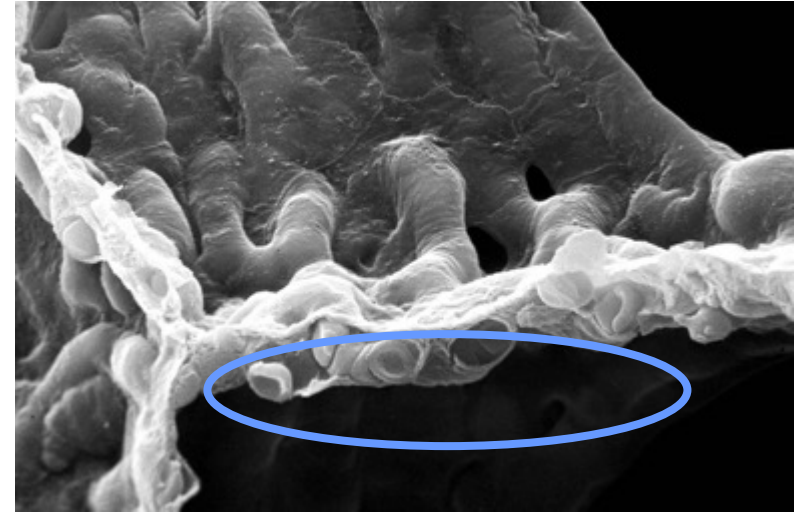
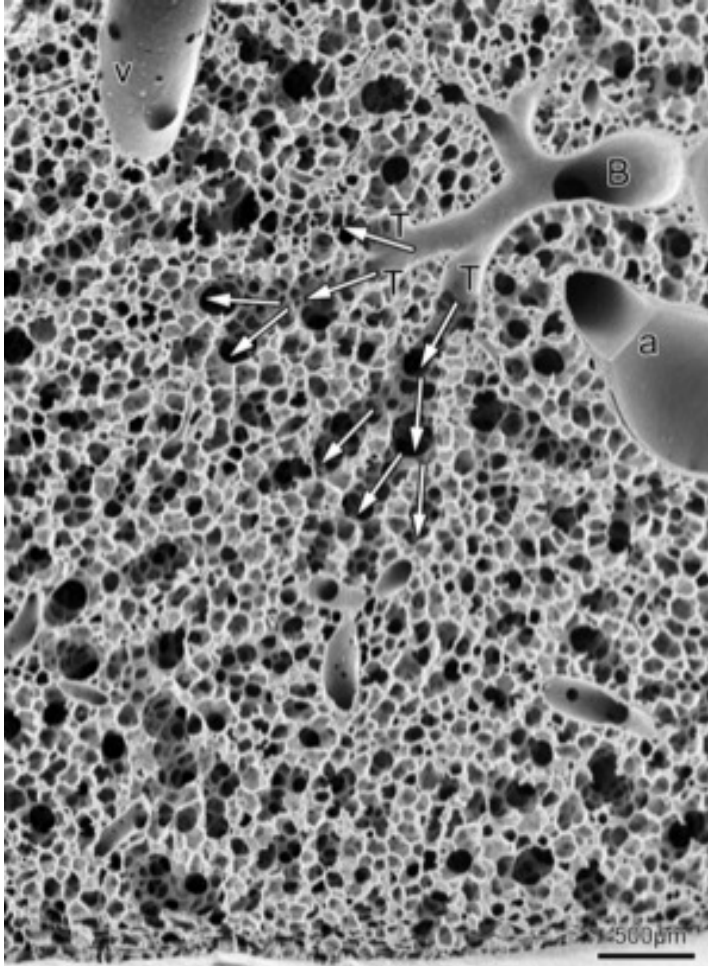
Function of the Lung

- Lung is responsible for gas exchange
- Respiration:
 - Inspiration of Oxygen
 - Expiration of CO₂
- Gas exchange
 - in alveoli
 - depends on lung parenchymal surface and thickness



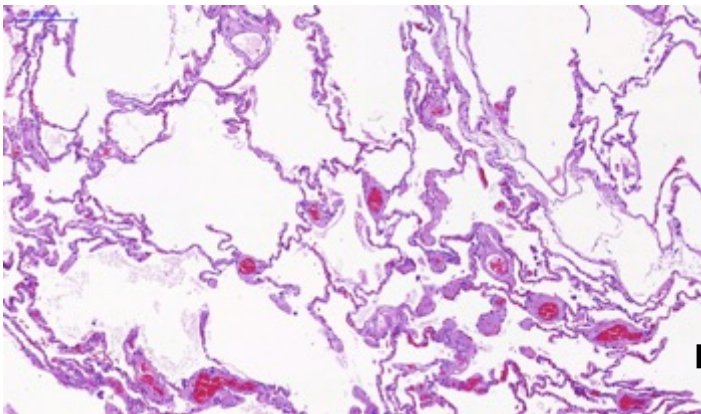
SCHÄFFLER, A., MENCHE, N. (Hrsg.): Biologie, Anatomie, Physiologie. Urban & Fischer, München (2000)]

Air-blood barrier

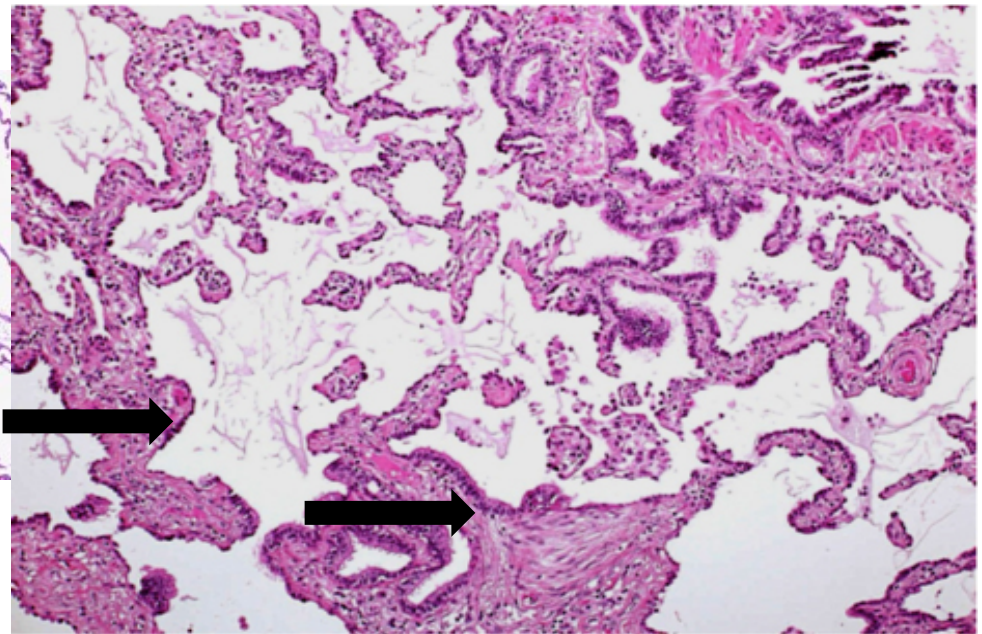


Interstitial lung diseases (ILD)

- Thickening of interstitial tissue
- Impairs gas exchange and oxygenation

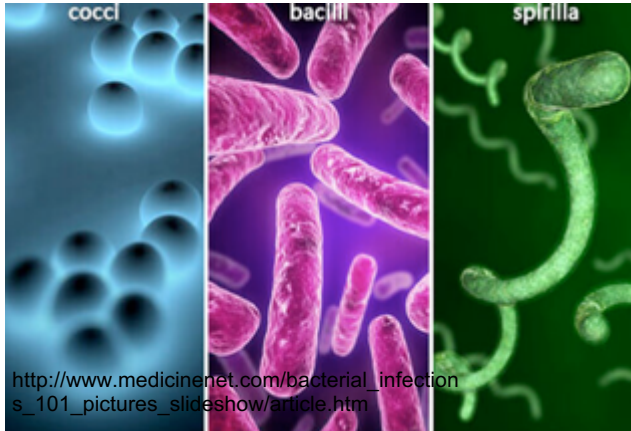


Dr. S. Berezowska, Pathologie Uni Bern



Risk factors for ILD

Infection and microbiome



Occupational exposure



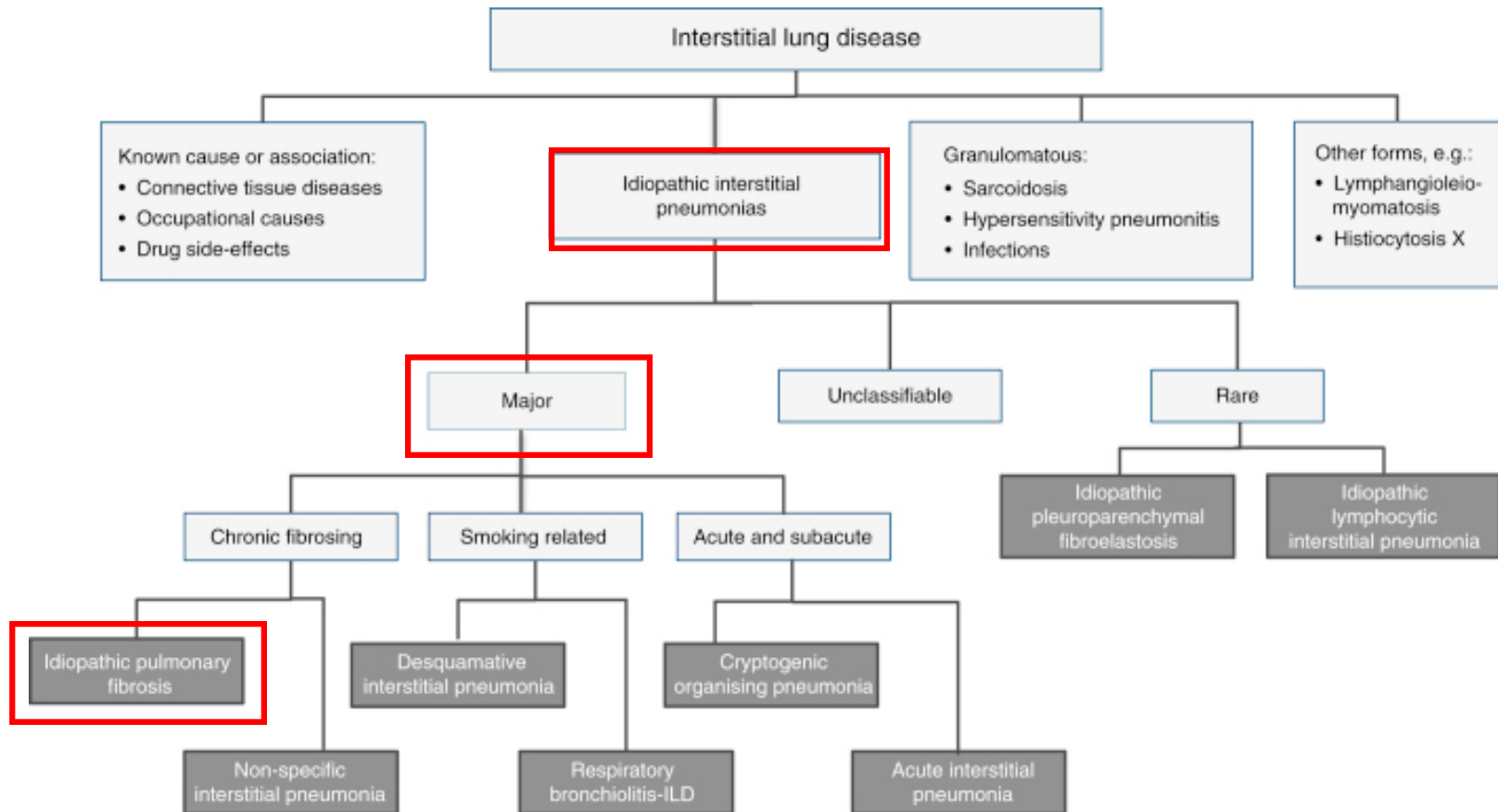
Smoking



Underlying Systemic Diseases



Classification of interstitial lung diseases

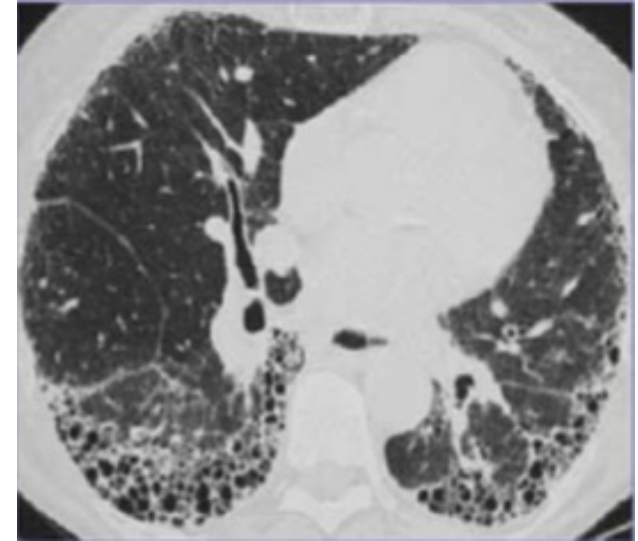


Zibrak JD et al. Interstitial lung disease: raising the index of suspicion in primary care. NPJ Prim Care Respir Med 2014; 24:14054.

Travis WD et al. An official American Thoracic Society/European Respiratory Society Statement: Update of the International Multidisciplinary Classification of the Idiopathic Interstitial Pneumonias. Am J Respir Crit Care Med Vol 188, Iss. 6, pp733-748, Sep 15, 2013.

Idiopathic pulmonary fibrosis

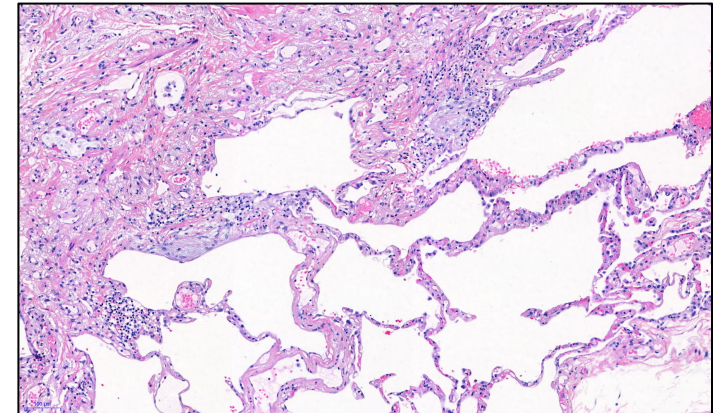
- Fatal lung disease
- Prognosis is extremely poor, no cure available
- The cause is not known
- unpredictable decline of lung function due to fibrosis
 - 1) ATS/ERS/JRS/ALAT. Am J Respir Crit Care Med 2011;183:788-824
 - 2) Am J Respir Crit Care Med. 2018 Sep 1;198(5):e44-e68



Guidelines

Respiration 2017;93:363–378
DOI: 10.1159/000464332

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Published online: March 25, 2017



Respiration

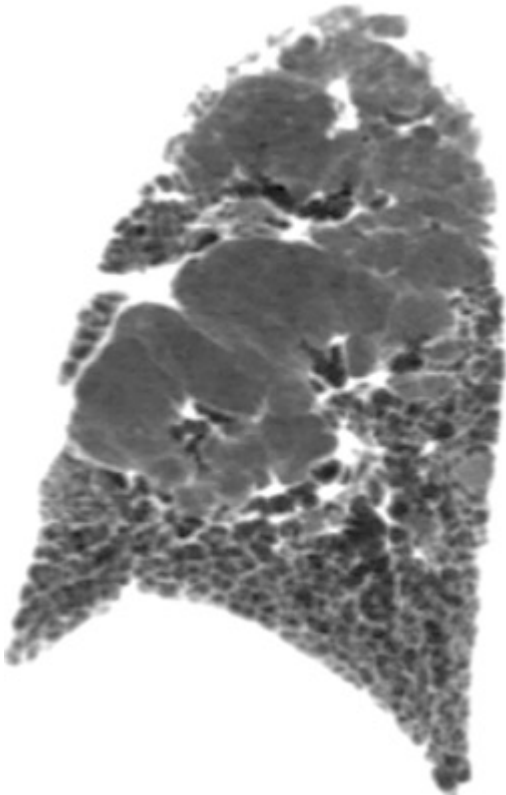
Idiopathic Pulmonary Fibrosis in Switzerland: Diagnosis and Treatment

Position Paper of the Swiss Working Group for Interstitial and Rare Lung Diseases of the Swiss Respiratory Society

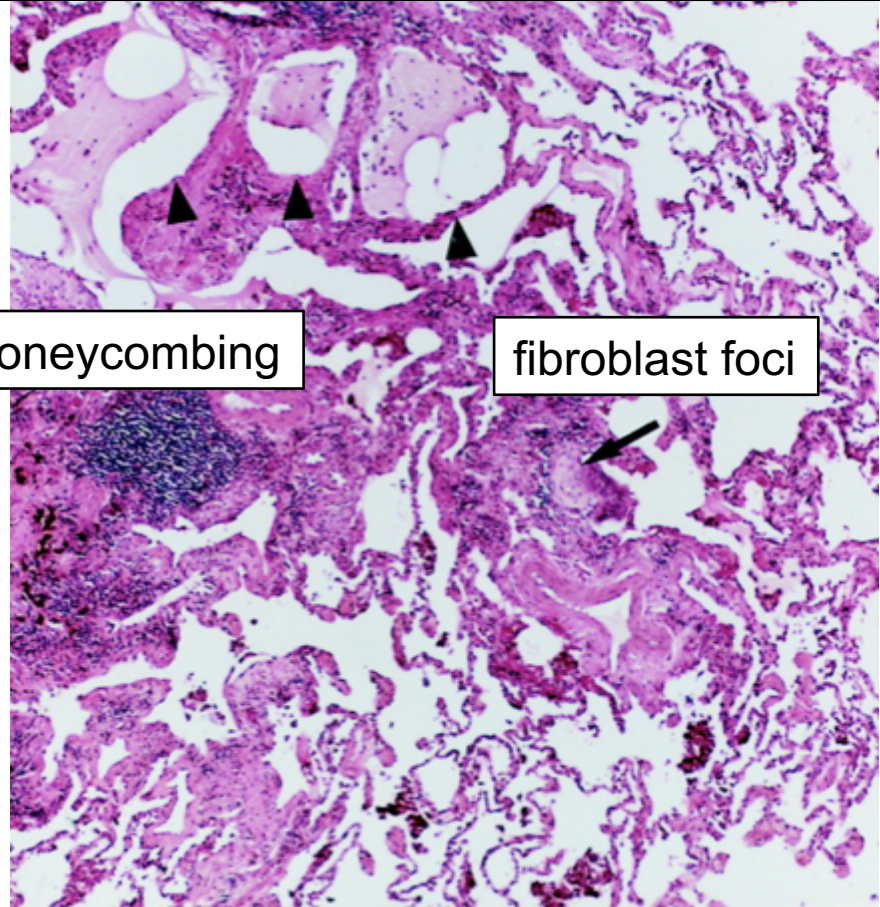
Manuela Funke-Chambour^a Andrea Azzola^b Dan Adler^c
Constance Barazzzone-Argiroffo^d Christian Benden^e Annette Boehler^f
Pierre-Olivier Bridevaux^g Martin Brutsche^h Christian F. Clarenbach^e
Katrín Hostettlerⁱ Rebekka Kleiner-Finger^g Laurent P. Nicod^j Paola M. Soccà^c
Michael Tammⁱ Thomas Geiser^a Romain Lazor^j

Idiopathische Lungenfibrose - Definition

Usual Interstitial Pneumonia- UIP



Hansell D M et al.
Radiology 2008;246:697-722



Katzenstein AL, Myers JL. State of the Art: Idiopathic pulmonary fibrosis: Clinical Relevance of pathological classification. AJRCCM Vol 157. pp 1301-1315, 1998.

Idiopathic Pulmonary Fibrosis.

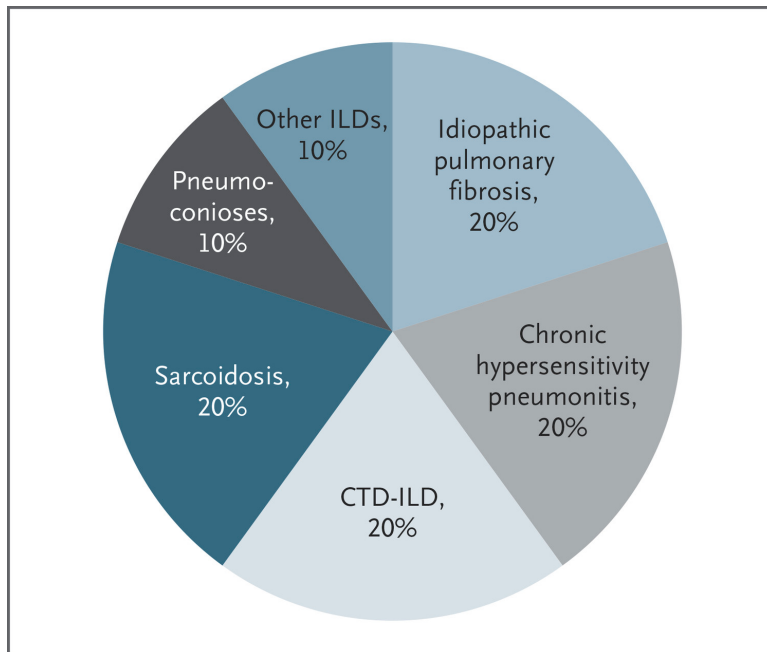


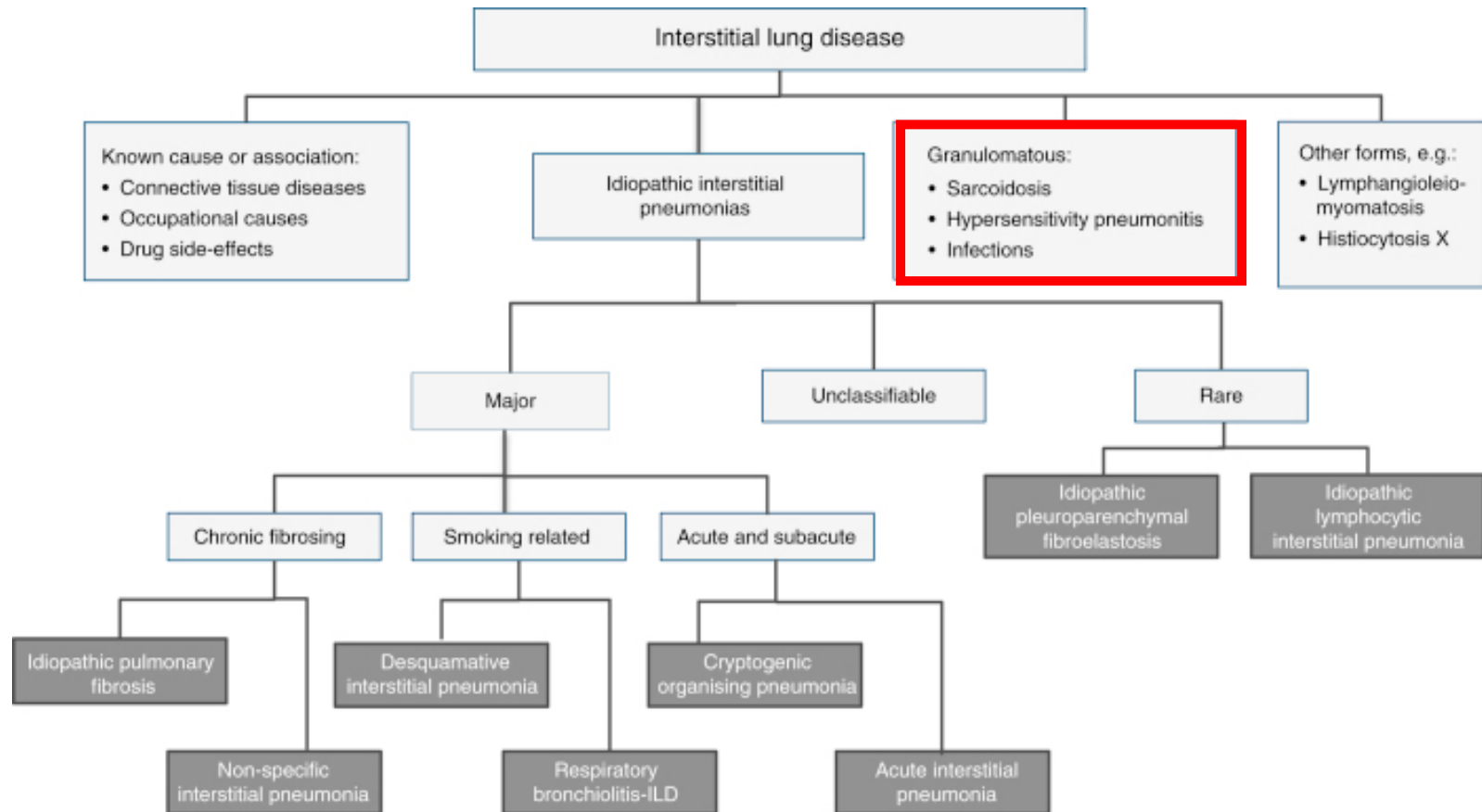
Table 2. Fibrotic Interstitial Lung Diseases (ILDs) of Known Cause That Mimic IPF.*

Condition	Examples or Causes	Clues from the Patient History
Chronic hypersensitivity pneumonitis	Mold, avian antigens, mycobacteria, isocyanates (specific exposures are often not identifiable)	Microbes in the home or workplace from forced-air heating, humidifiers, hot tubs, water damage, or visible mold; indoor or caged birds, down or feather bedding, agricultural exposure
Connective-tissue disease–related ILDs	Rheumatoid arthritis, systemic sclerosis, idiopathic inflammatory myopathy (e.g., anti-synthetase syndrome), Sjögren's syndrome	Joint pain, stiffness, or swelling; skin thickening or tightening; rash; dry eyes; dry mouth; heartburn; muscle pain or tenderness; Raynaud's phenomenon
Drug-induced ILDs	Amiodarone, methotrexate, nitrofurantoin, chemotherapeutic agents	Medication history
Pneumoconiosis (occupational ILDs)	Asbestosis, coal workers' pneumoconiosis, silicosis, berylliosis	Occupational history and exposures

* ANA denotes antinuclear antibodies, anti-CCP anti-cyclic citrullinated peptide antibodies, CK creatine kinase.

† Crackles are noted on lung examination in nearly all cases. Reticulation with or without traction bronchiectasis is present in nearly all cases.

Classification of interstitial lung diseases



Zibrak JD et al. Interstitial lung disease: raising the index of suspicion in primary care. NPJ Prim Care Respir Med 2014; 24:14054.

Travis WD et al. An official American Thoracic Society/European Respiratory Society Statement: Update of the International Multidisciplinary Classification of the Idiopathic Interstitial Pneumonias. Am J Respir Crit Care Med Vol 188, Iss. 6, pp733-748, Sep 15, 2013.

Hypersensitivity pneumonitis - HP

Exogen allergic alveolitis - EAA

- Results from repeated exposure to various organic particles
- acute, subacute, chronic forms

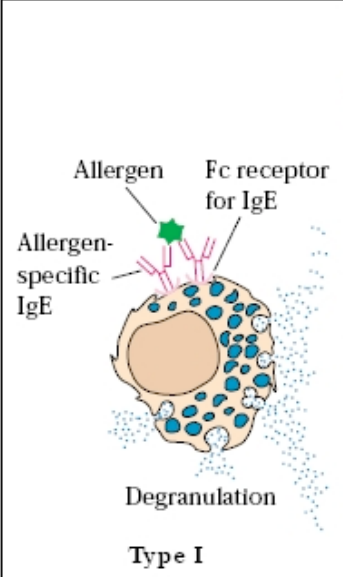
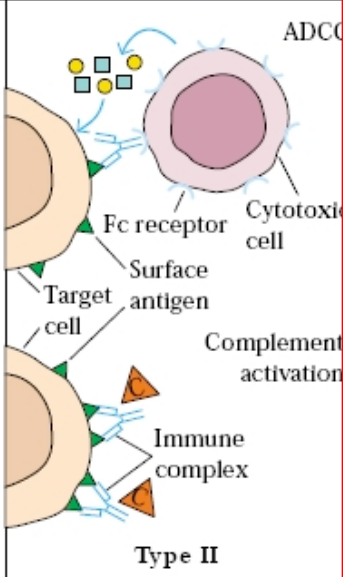
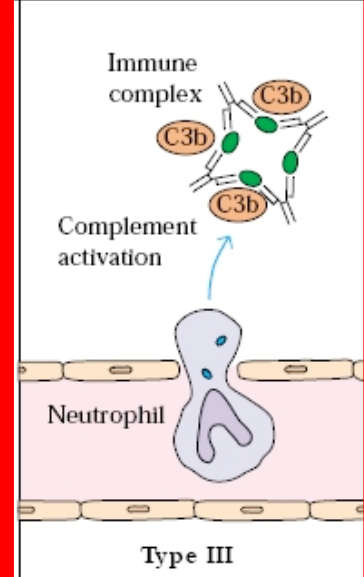
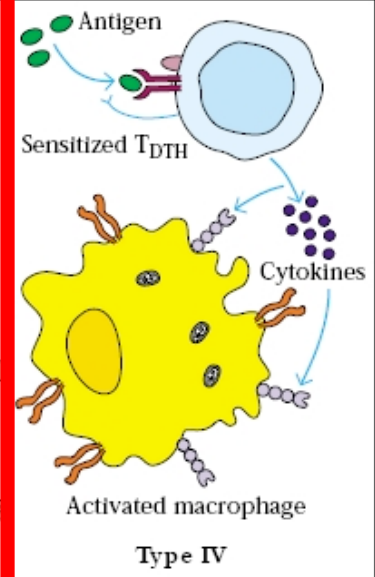
Etiological agents of HP

Disease	Antigen	Source
Fungal and bacterial		
Farmer's lung	<i>Saccharopolyspora rectivirgula</i>	Moldy hay, grain, silage
Ventilation pneumonitis; humidifier lung; air conditioner lung	<i>Thermoactinomyces vulgaris</i> , <i>Thermoactinomyces sacchari</i> , <i>Thermoactinomyces candidus</i> , <i>Klebsiella oxytoca</i>	Contaminated forced-air systems; water reservoirs
Bagassosis	<i>T. vulgaris</i>	Moldy sugarcane (i.e., bagasse)
Mushroom worker's lung	<i>T. sacchari</i>	Moldy mushroom compost
Enoki mushroom worker's lung (Japan)	<i>Penicillium citrinum</i>	Moldy mushroom compost
Suberosis	<i>Thermoactinomyces viridis</i> , <i>Aspergillus fumigatus</i> , <i>Penicillium frequentans</i> , <i>Penicillium glabrum</i>	Moldy cork
Detergent lung; washing powder lung	<i>Bacillus subtilis</i> enzymes	Detergents (during processing or use)
Malt worker's lung	<i>Aspergillus fumigatus</i> , <i>Aspergillus clavatus</i>	Moldy barley
Sequoiosis	<i>Graphium</i> , <i>Pullularia</i> , and <i>Trichoderma</i> spp., <i>Aureobasidium pullulans</i>	Moldy wood dust
Maple bark stripper's lung	<i>Cryptostroma corticale</i>	Moldy maple bark
Cheese washer's lung	<i>Penicillium casei</i> , <i>A. clavatus</i>	Moldy cheese
Woodworker's lung	<i>Alternaria</i> spp., wood dust	Oak, cedar, and mahogany dust, pine and spruce pulp
Hardwood worker's lung	<i>Paecilomyces</i>	Kiln-dried wood
Paprika slicer's lung	<i>Mucor stolonifer</i>	Moldy paprika pods
Sauna taker's lung	<i>Aureobasidium</i> spp., other sources	Contaminated sauna water
Familial HP	<i>B. subtilis</i>	Contaminated wood dust in walls

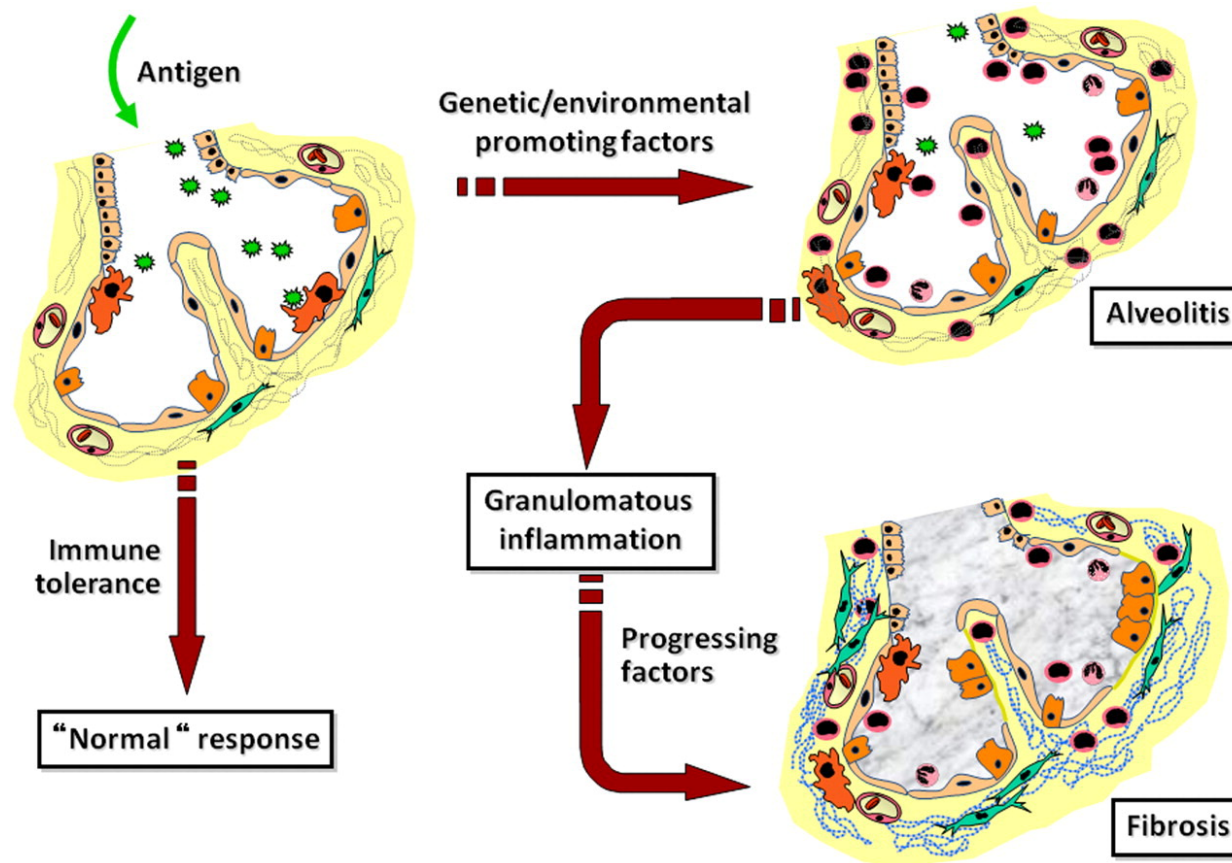
Selman M et al. Hypersensitivity pneumonitis. Insights in diagnosis and pathobiology. Am J Respir Crit Care Med Vol. 186, Iss. 4 pp 314-324, Aug 15, 2012

Disease	Antigen	Source
Fungal and bacterial		
Wood trimmer's lung	<i>Rhizopus</i> spp., <i>Mucor</i> spp.	Contaminated wood trimmings
Composter's lung	<i>T. vulgaris</i> , <i>Aspergillus</i>	Compost
Basement shower HP	<i>Epicoccum nigrum</i>	Mold on unventilated shower
Hot tub lung	<i>Mycobacterium avium complex</i>	Hot tub mists; mold on ceiling
Wine maker's lung	<i>Botrytis cinerea</i>	Mold on grapes
Woodsman's disease	<i>Penicillium</i> spp.	Oak and maple trees
Thatched roof lung	<i>Saccharomonospora viridis</i>	Dead grasses and leaves
Tobacco grower's lung	<i>Aspergillus</i> spp.	Tobacco plants
Potato riddler's lung	<i>Thermophilic actinomycetes</i> , <i>S. rectivirgula</i> , <i>T. vulgaris</i> , <i>Aspergillus</i> spp.	Moldy hay around potatoes
Summer-type pneumonitis	<i>Trichosporon cutaneum</i>	Contaminated old houses
Dry rot lung	<i>Merulius lacrymans</i>	Rotten wood
Stipatosis	<i>Aspergillus fumigatus</i> ; <i>T. actinomycetes</i>	Esparto dust
Machine operator's lung	<i>Mycobacterium immunogenum</i> ; <i>Pseudomonas fluorescens</i>	Aerosolized metalworking fluid
Residential provoked pneumonitis Amebae	<i>Aureobasidium pullulans</i>	Residential exposure
Humidifier lung	<i>Naegleria gruberi</i> , <i>Acanthamoeba polyphaga</i> , <i>Acanthamoeba castellanii</i> , <i>Bacillus</i> sp., others	Contaminated water from home humidifier, ultrasonic misting fountains
Shower curtain disease	<i>Phoma violacea</i>	Moldy shower curtain
Animal proteins		
Pigeon breeder's or pigeon fancier's disease	Avian droppings, feathers, serum	Parakeets, budgerigars, pigeons, chickens, turkeys
Pituitary snuff taker's lung	Pituitary snuff	Bovine and porcine pituitary proteins
Fish meal worker's lung	Fish meal	Fish meal dust
Bat lung	Bat serum protein	Bat droppings
Furrier's lung	Animal fur dust	Animal pelts
Animal handler's lung; laboratory worker's lung	Rats, gerbils	Urine, serum, pelts, proteins
Insect proteins		
Miller's lung	<i>Sitophilus granarius</i> (i.e., wheat weevil)	Dust-contaminated grain
Lycoperdonosis	Puffball spores	Lycoperdon puffballs

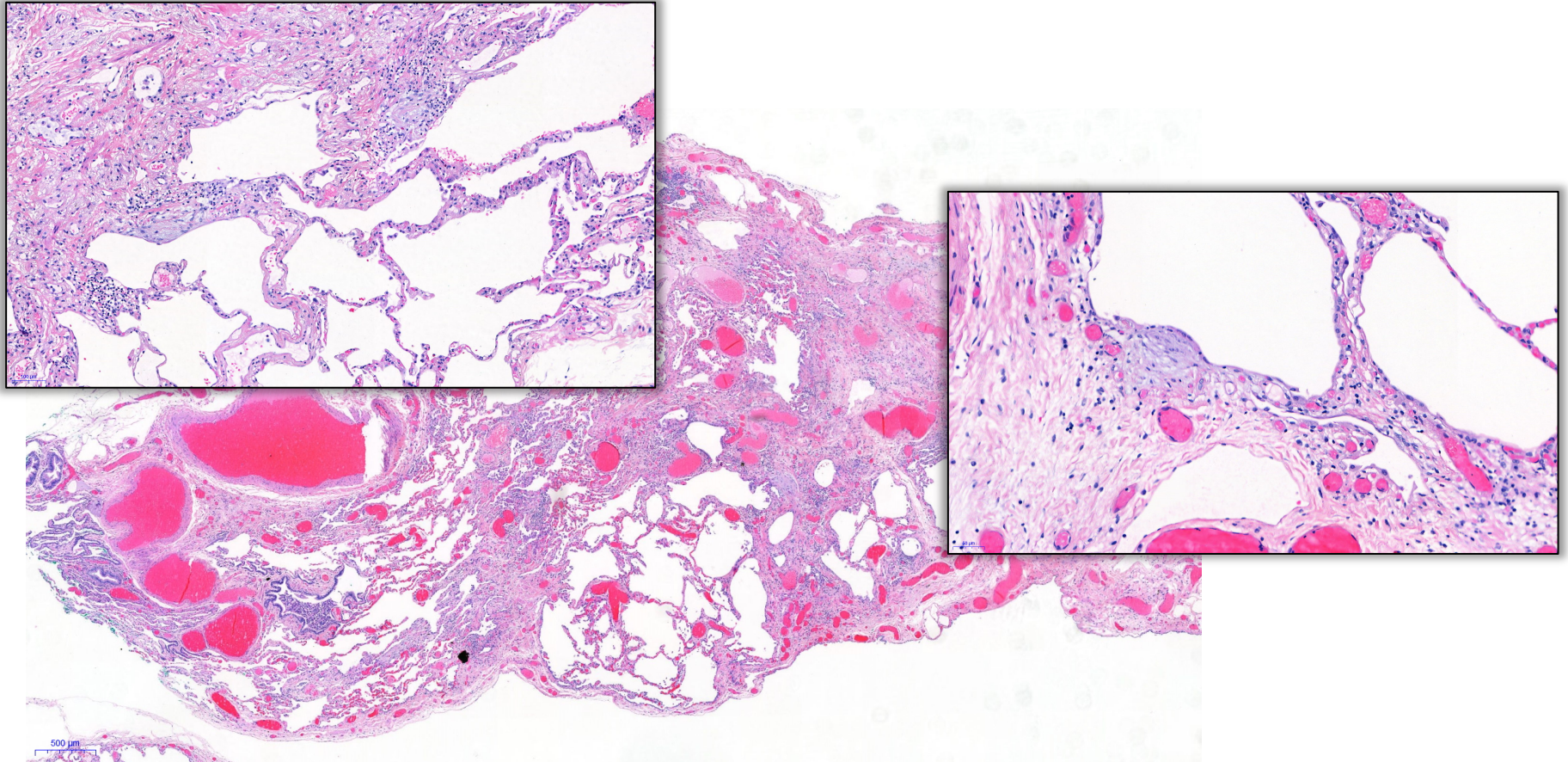
Hypersensitivity pneumonitis: pathogenesis

 Type I	 Type II	 Type III	 Type IV
IgE-Mediated Hypersensitivity	IgG-Mediated Cytotoxic Hypersensitivity	Immune Complex-Mediated Hypersensitivity	Cell-Mediated Hypersensitivity
Ag induces crosslinking of IgE bound to mast cells and basophils with release of vasoactive mediators	Ab directed against cell surface antigens mediates cell destruction via complement activation or ADCC	Ag-Ab complexes deposited in various tissues induce complement activation and an ensuing inflammatory response mediated by massive infiltration of neutrophils	Sensitized T _H 1 cells release cytokines that activate macrophages or T _C cells which mediate direct cellular damage

Hypersensitivity pneumonitis – HP: pathogenesis

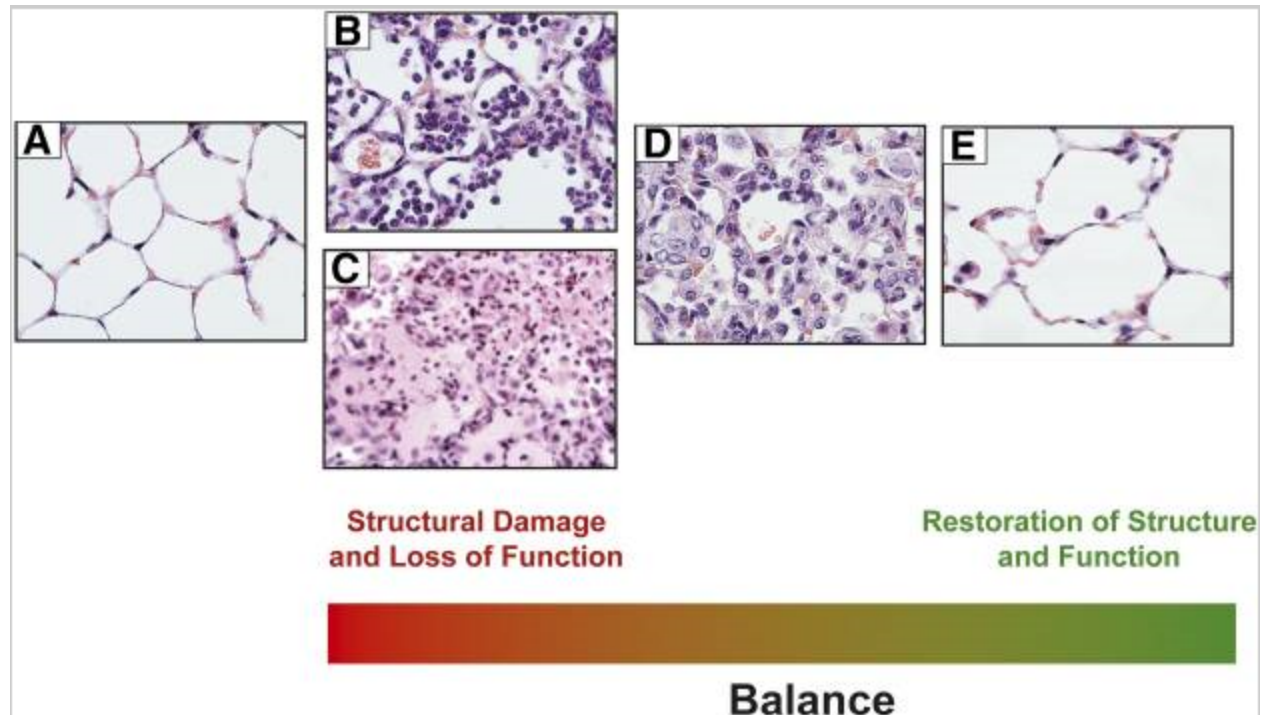


Pulmonary Lungenfibrose - Pathogenesis

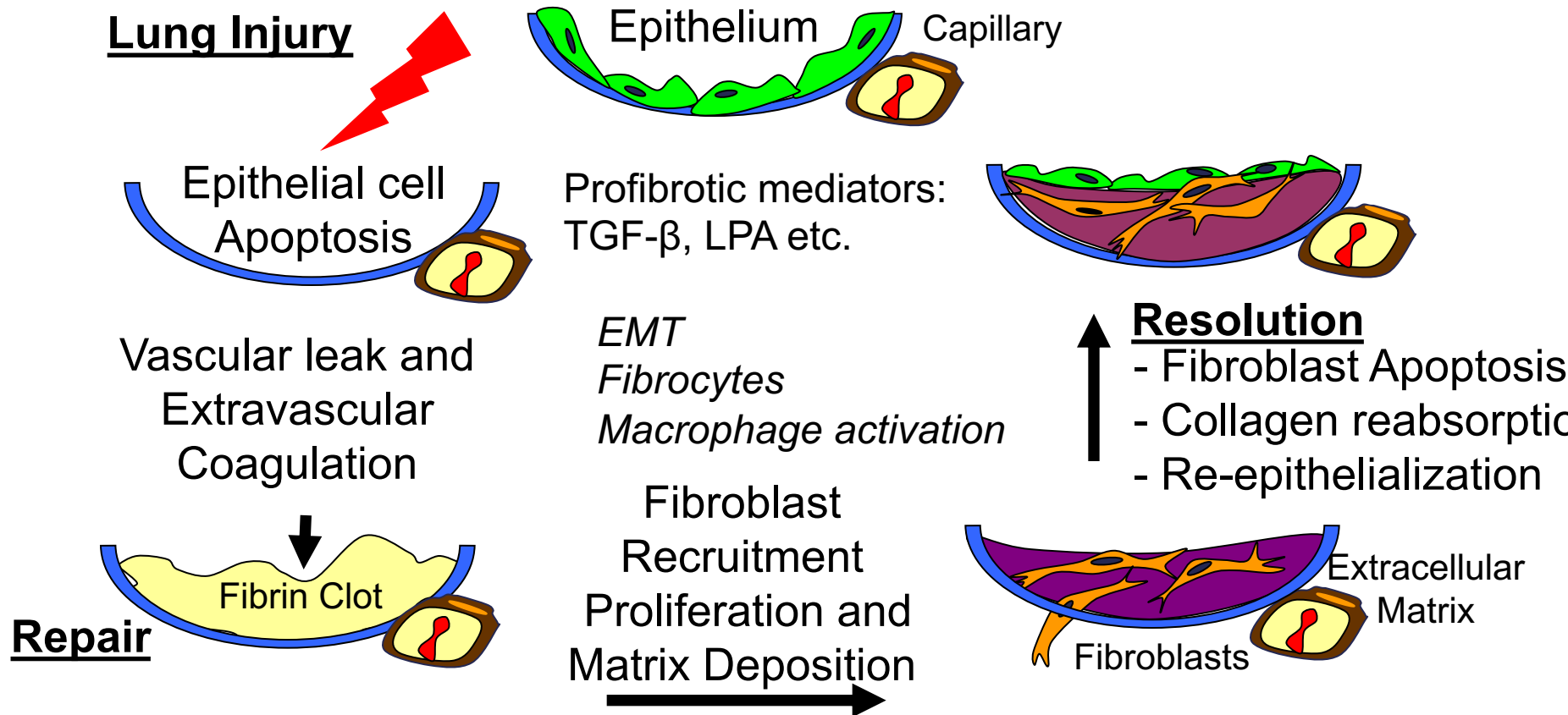


Courtesy of Sabina Berezowska

Lung injury and normal wound healing

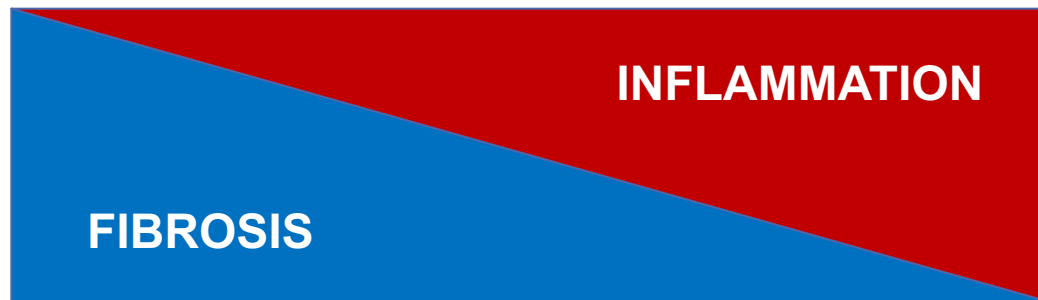


Injury with Abnormal Repair

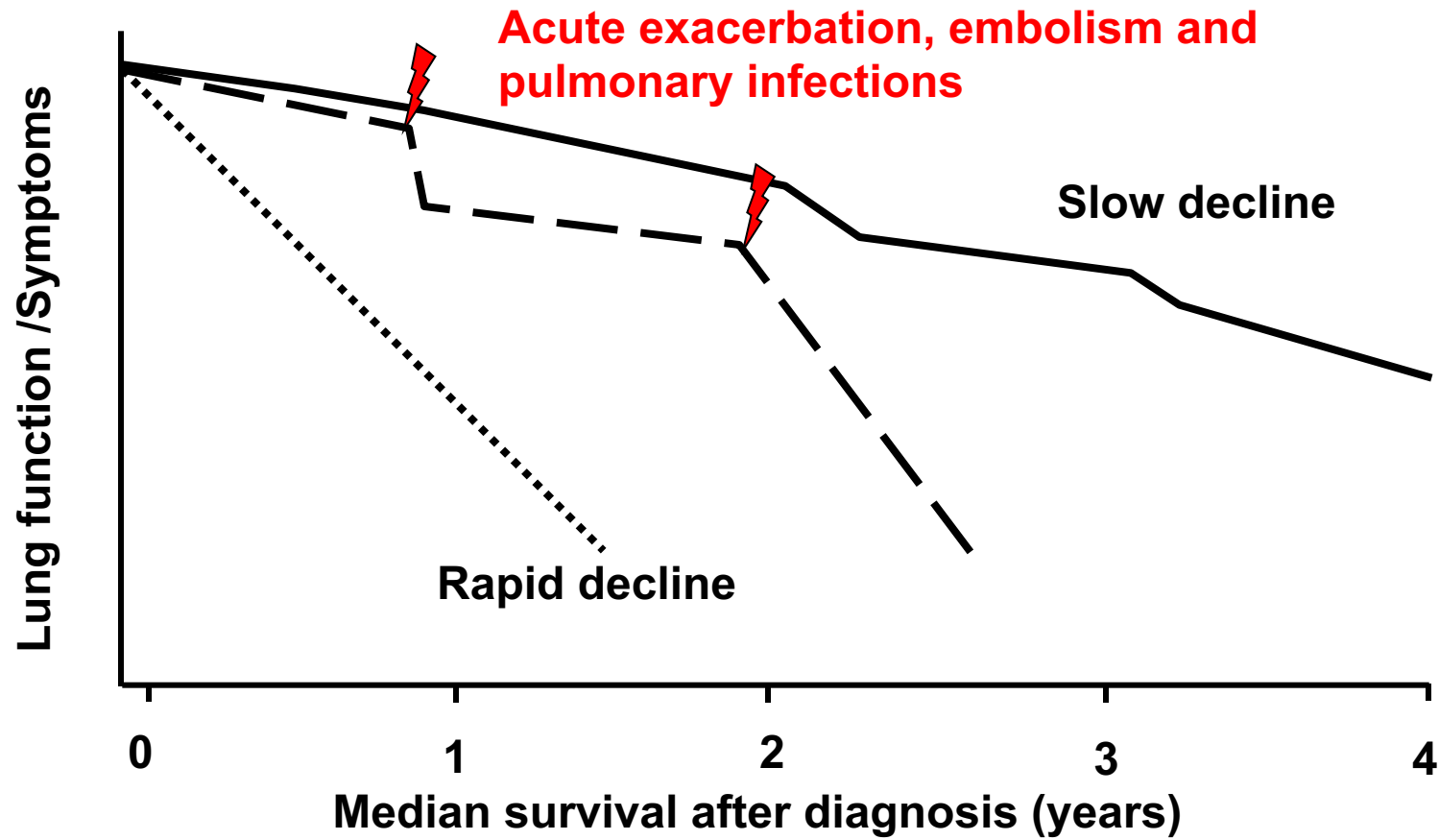


**Dysregulation of any of these responses
can contribute to fibrosis**

CAUSES OF LUNG FIBROSIS



Unpredictable clinical course of IPF



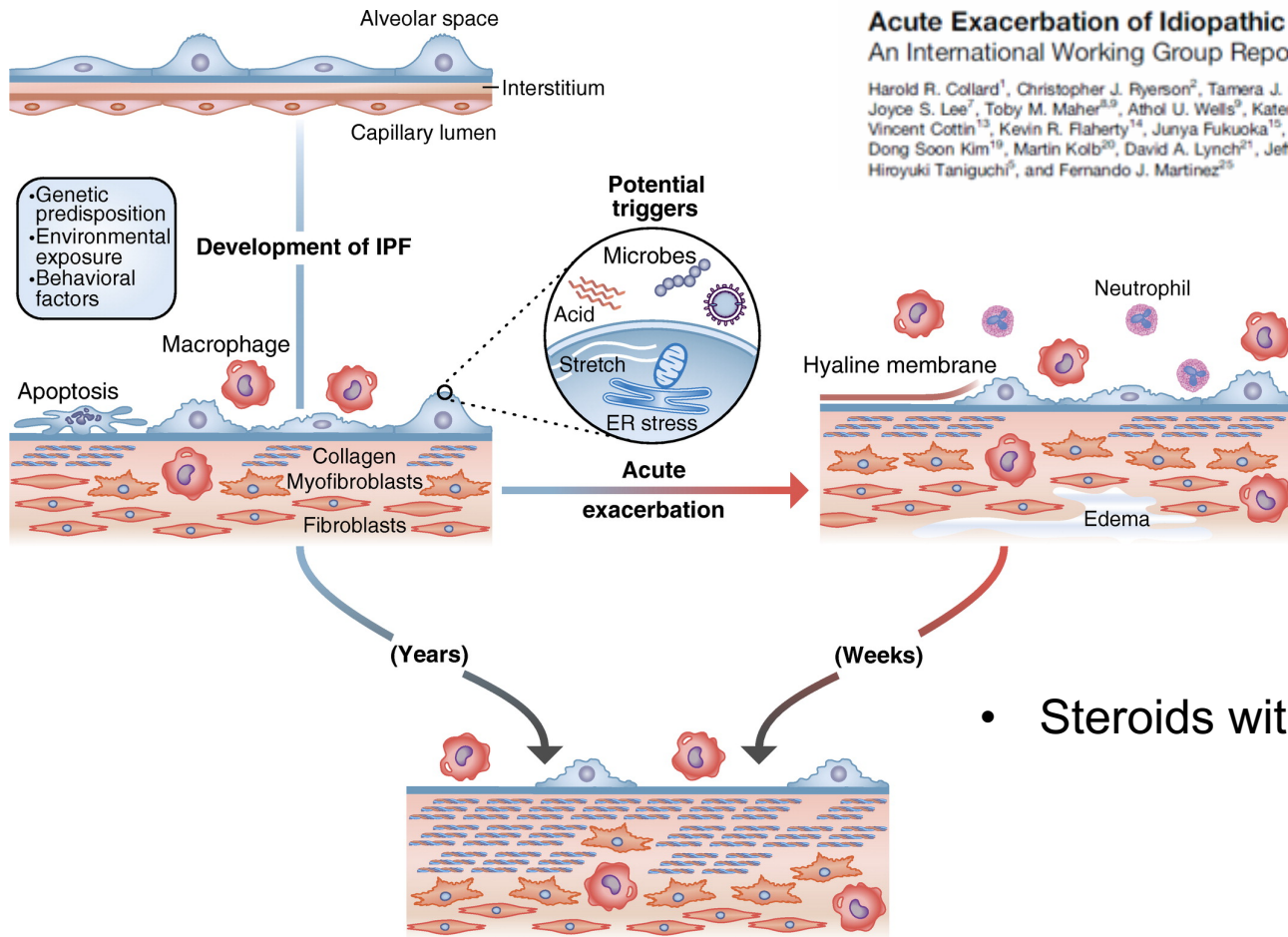
Acute IPF exacerbation

CONCISE CLINICAL REVIEW



Acute Exacerbation of Idiopathic Pulmonary Fibrosis An International Working Group Report

Harold R. Collard¹, Christopher J. Ryerson², Tamera J. Corte³, Gisli Jenkins⁴, Yasuhiro Kondoh⁵, David J. Lederer⁶, Joyce S. Lee⁷, Toby M. Maher^{8,9}, Athol U. Wells⁹, Katerina M. Antoniou¹⁰, Juergen Behr¹¹, Kevin K. Brown¹², Vincent Cottin¹³, Kevin R. Flaherty¹⁴, Junya Fukuda¹⁵, David M. Hansell¹⁶, Takeshi Johkoh¹⁷, Naftali Kaminski¹⁸, Dong Soon Kim¹⁹, Martin Kolb²⁰, David A. Lynch²¹, Jeffrey L. Myers²², Ganesh Raghu²³, Luca Richeldi²⁴, Hiroyuki Taniguchi⁵, and Fernando J. Martinez²⁵



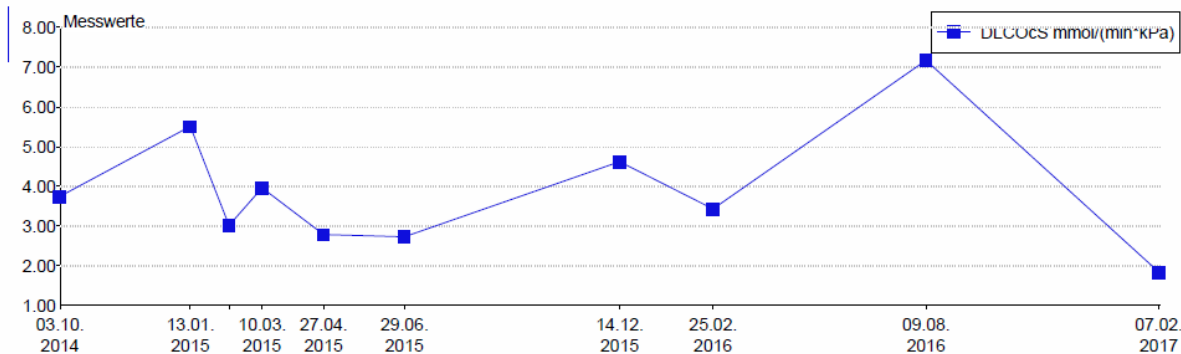
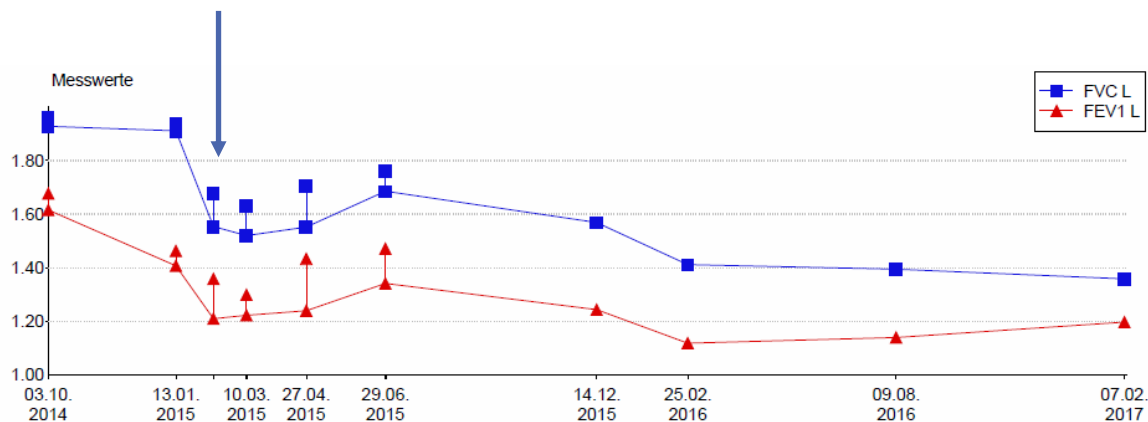
- Steroids without scientific proof

Am J Respir Crit Care Med. 2016 Aug 1;194(3):265-75.

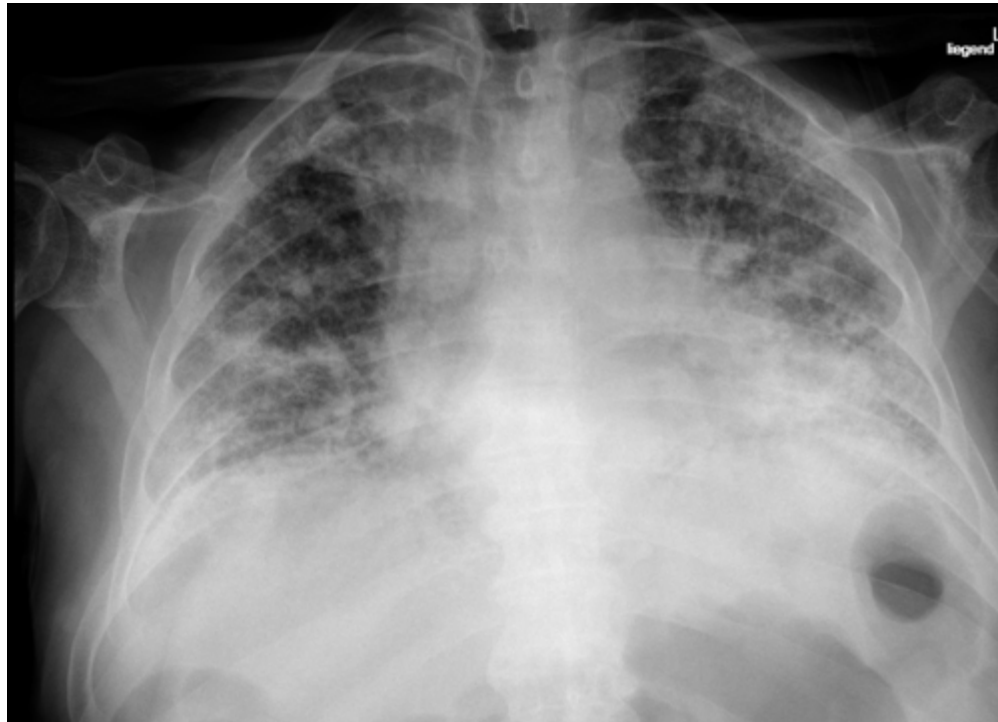
Idiopathic pulmonary fibrosis (IPF)- patient 1

- Male patient, born 1960
- Diagnosed with IPF 2015 (Wedge Biopsy)

Nintedanib



Idiopathic pulmonary fibrosis (IPF)- patient 1



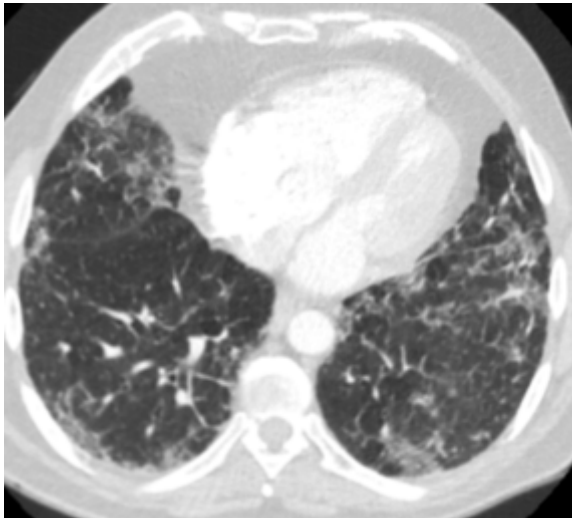
Pneumonia (left)

Died Mai 2017 due to respiratory failure

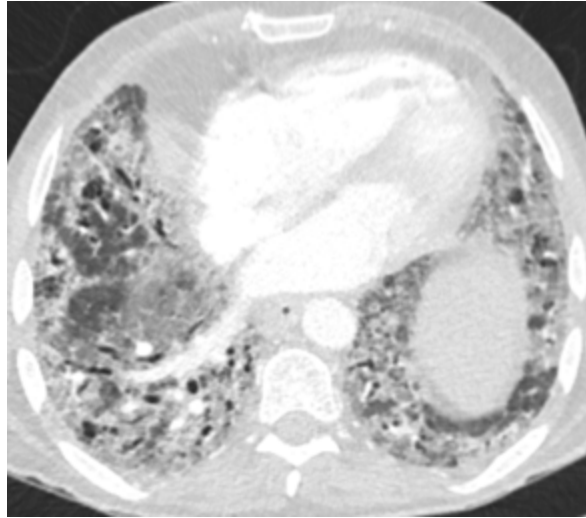
Idiopathic pulmonary fibrosis (IPF)- patient 2

Male, born 1945

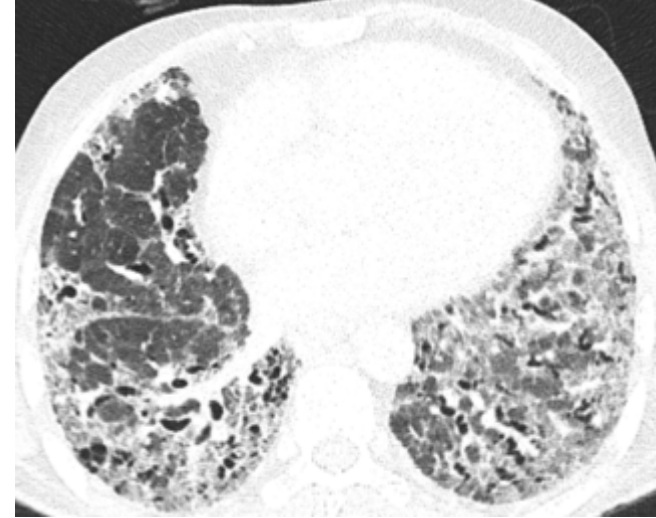
09/2016



03/2017



04/2017



Fibrosis progression after pneumonia in IPF

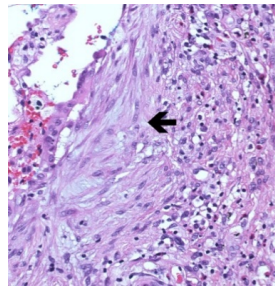
Pulmonary infections (Pneumonia)

Pneumonia patient



Usually no fibrosis

IPF patient



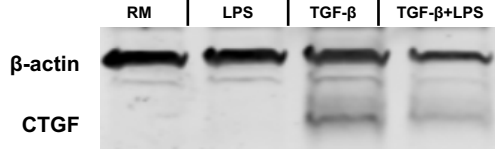
Fibrosis progression

Why is the response different?

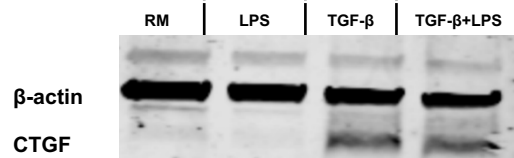
TLR4 activation by LPS reduces profibrotic markers in fibroblasts from controls via Smad3

CTGF

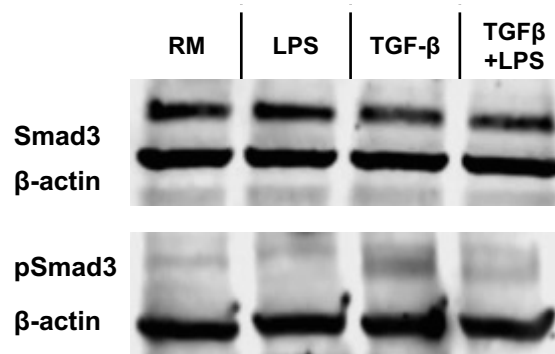
control



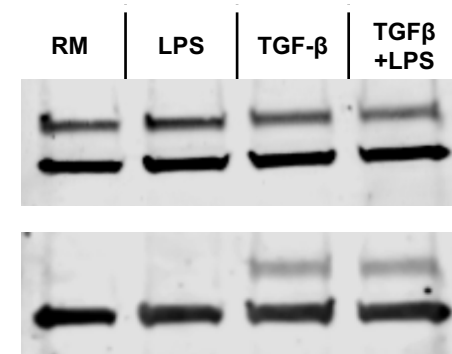
IPF



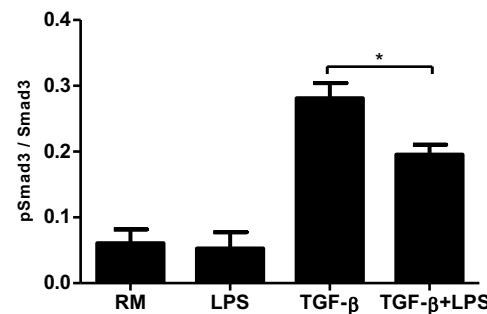
Control fibroblasts



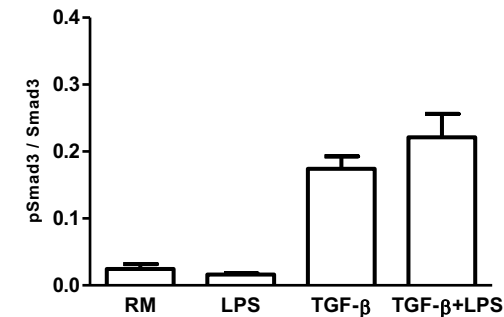
IPF fibroblasts



Quantification pSmad3/Smad3

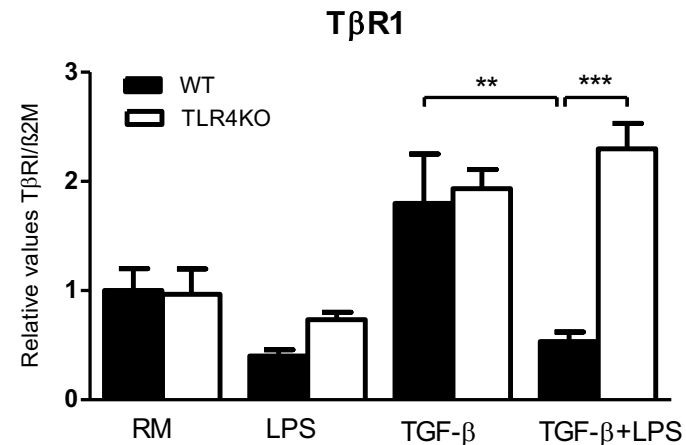
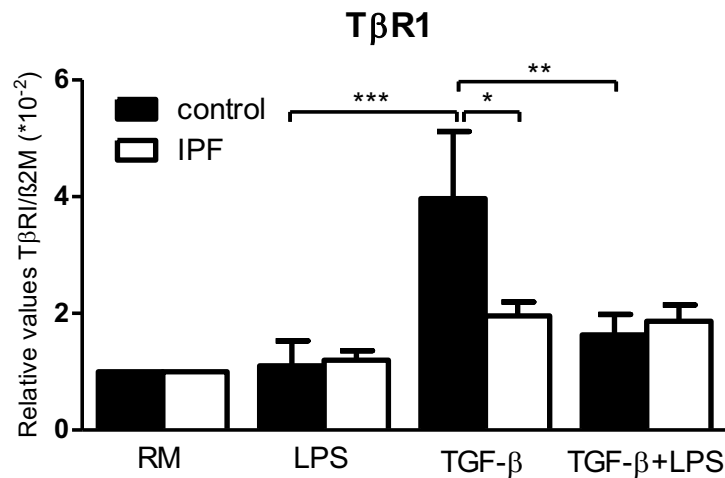


Quantification pSmad3/Smad3



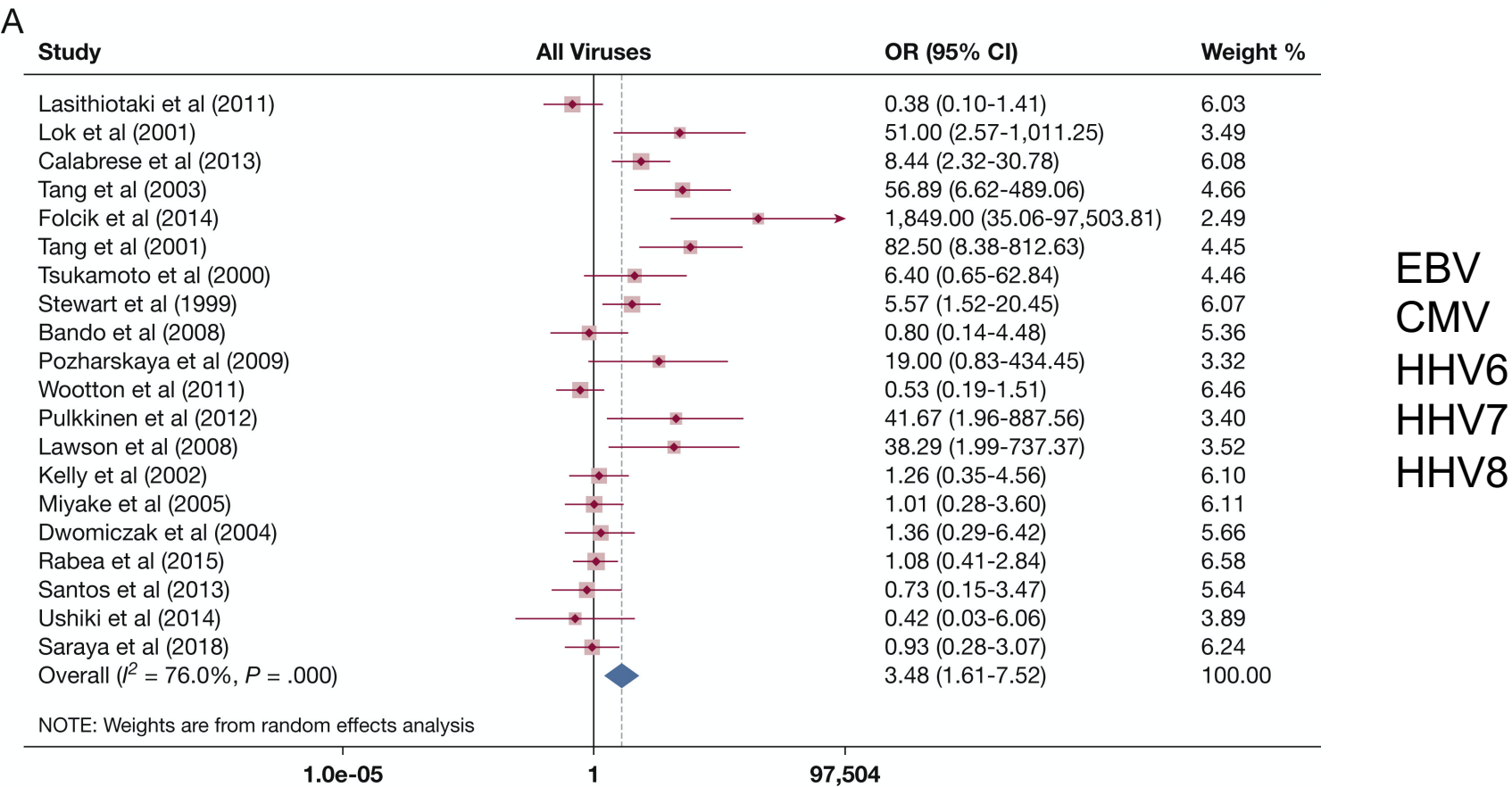
Ebener S, Barnowski S, Wotzkow C, Marti TM, Elena Lodriguez, Crestani B, Blank F, Schmid RA, Geiser T, **Funke M**.
Toll-like receptor 4 (TLR4) activation attenuates pro-fibrotic response in control fibroblasts but not fibroblasts from IPF patients.
Am J Physiol Lung Cell Mol Physiol. 2017 Jan 1;312(1):L42-L55.

TGF-beta receptor expression is reduced after TLR4 stimulation in controls and depends on TLR4



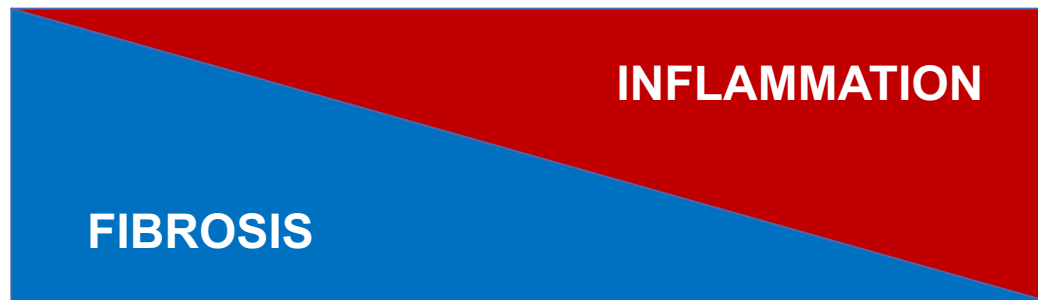
Ebener S, Barnowski S, Wotzkow C, Marti TM, Elena Lodriguez, Crestani B, Blank F, Schmid RA, Geiser T, **Funke M**.
Toll-like receptor 4 (TLR4) activation attenuates pro-fibrotic response in control fibroblasts but not fibroblasts from IPF patients. *Am J Physiol Lung Cell Mol Physiol*. 2017 Jan 1;312(1):L42-L55.

Viral infections can increase risk for pulmonary fibrosis



Sheng G, Chen P, Wei Y, *et al.* Viral Infection Increases the Risk of Idiopathic Pulmonary Fibrosis: A Meta-Analysis, *Chest* 2019. (doi: 10.1016/j.chest.2019.10.032.)

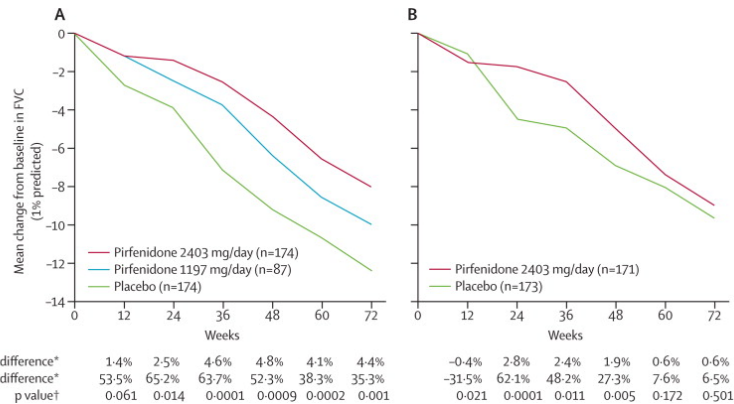
CAUSES OF LUNG FIBROSIS



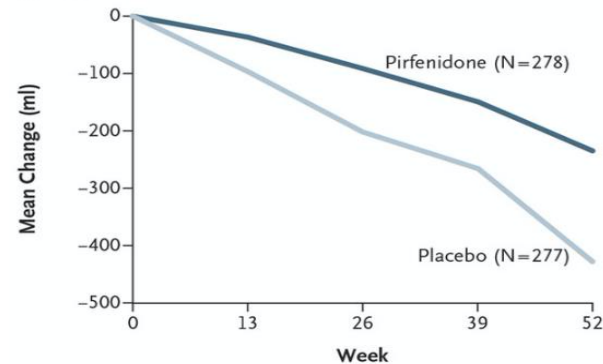
Treatment of fibrotic lung diseases

Pirfenidone

CAPACITY



ASCEND



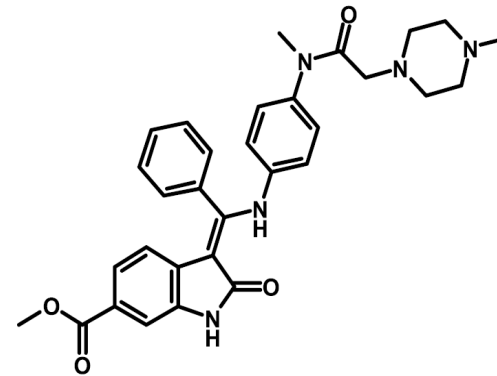
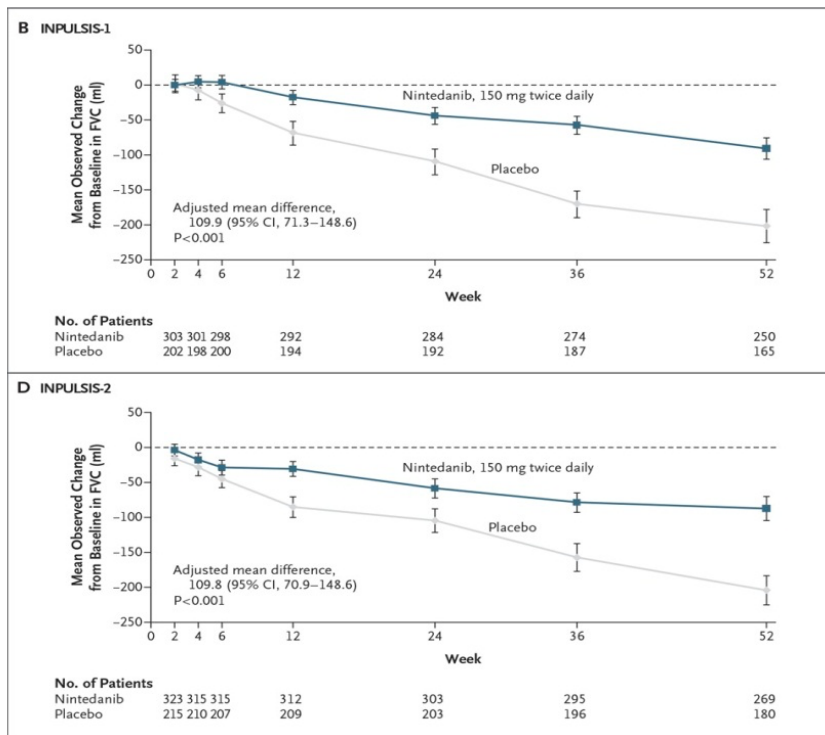
Delta → 193 ml

Noble PW et al. Lancet 2011;377:1760–1769.

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

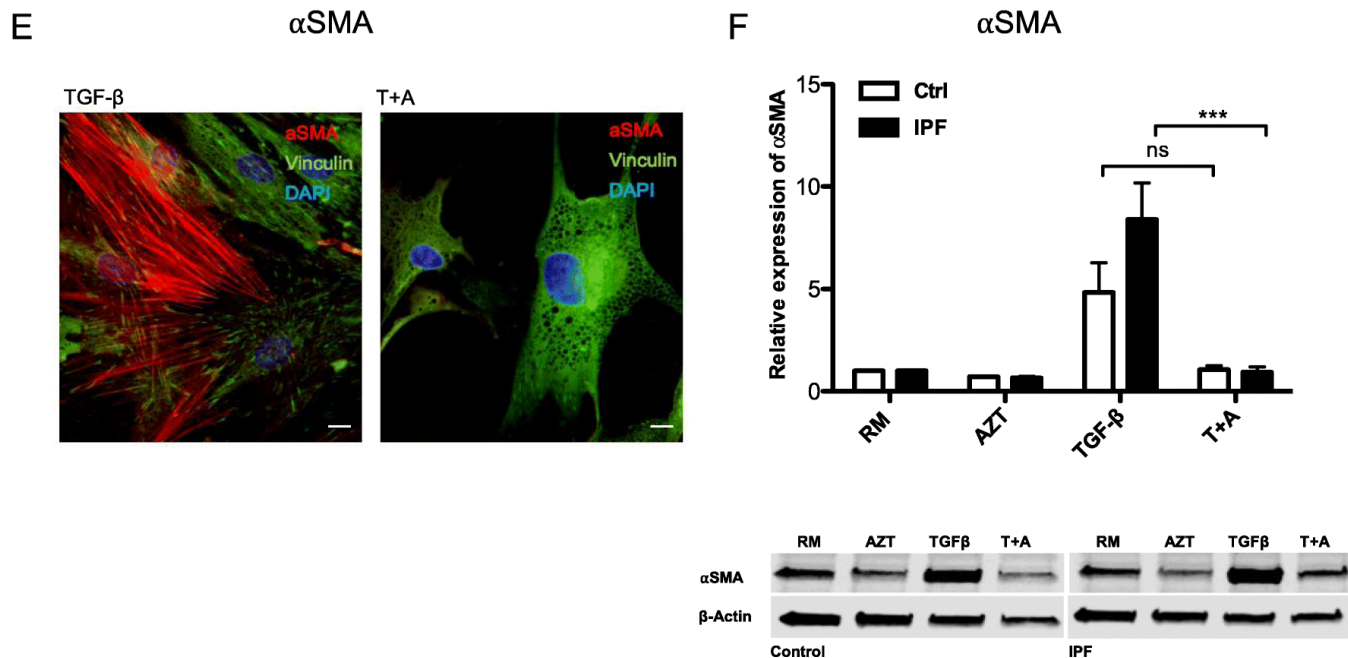
Treatment of fibrotic lung diseases

Nintedanib



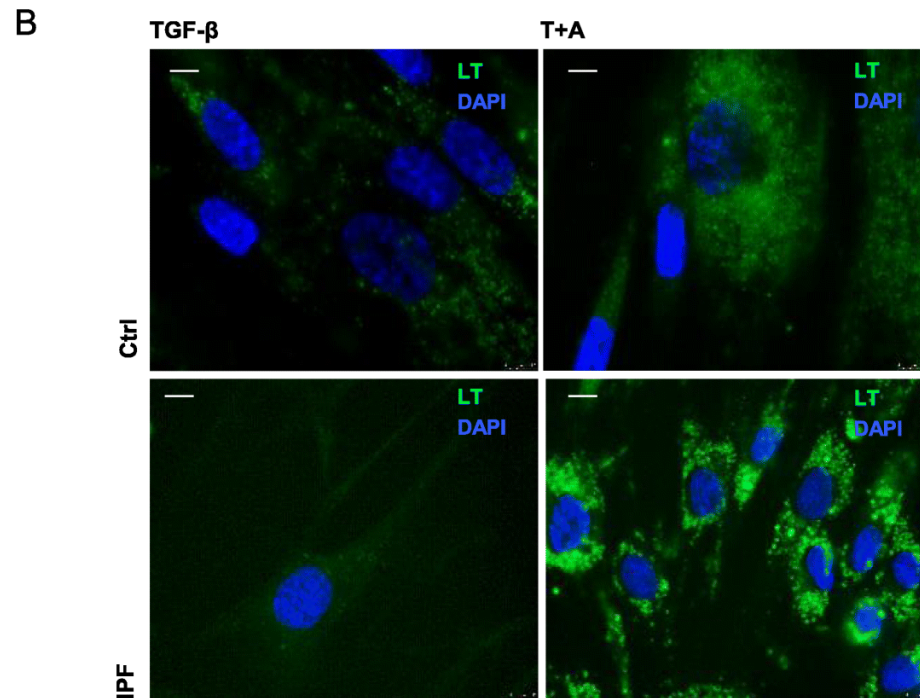
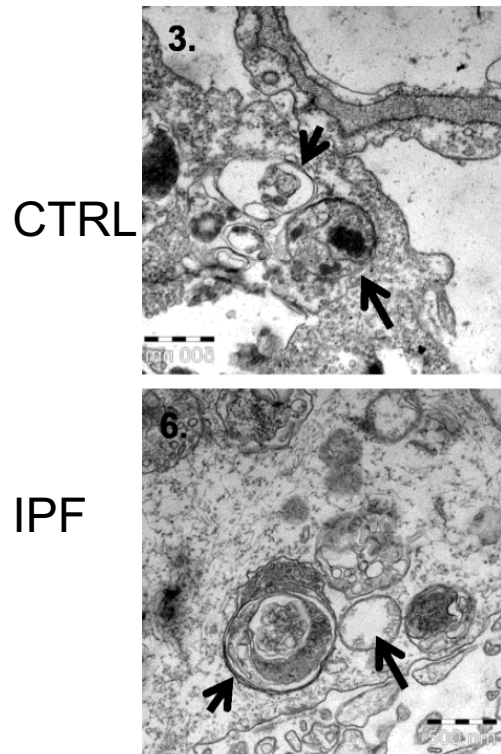
Richeldi L et al. N Engl J Med 2014.

New treatment approaches



Krempaska K, Barnowski S, Gavini J, Hobi N, Ebener S, Simillion C, Stokes A, Schliep R, Knudsen L, Geiser TK, Funke-Chambour M. Azithromycin has enhanced effects on lung fibroblasts from idiopathic pulmonary fibrosis (IPF) patients compared to controls. *Resp Res* 2020 Jan 15;21(1):25.

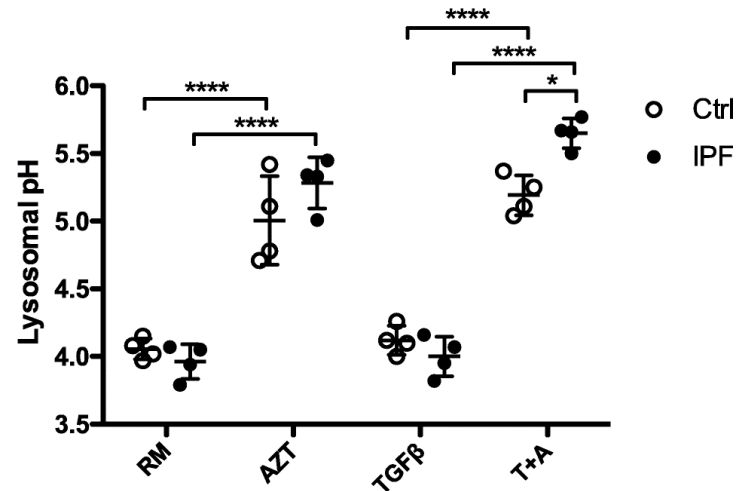
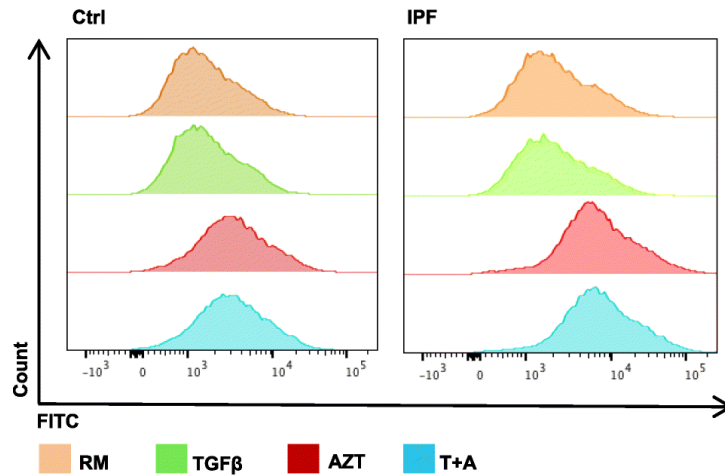
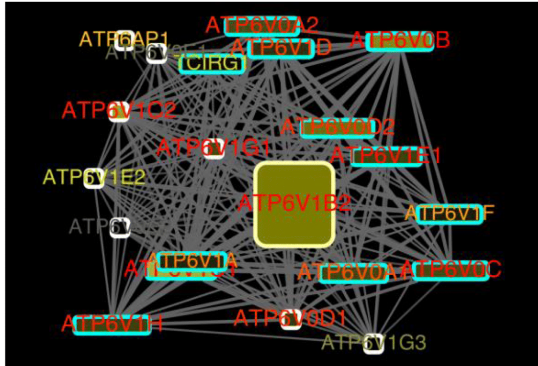
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Conclusions

- Inflammation and infection influence disease course in lung fibrosis
- Inflammatory receptors and regulators are involved in fibrosis development and progression
- New approaches are needed to improve mortality, specifically after pulmonary infection in patients with pulmonary fibrosis

SWISS-IIP

Sprechstunde für interstitielle
Lungenerkrankungen und
Sarkoidose

Merci!

