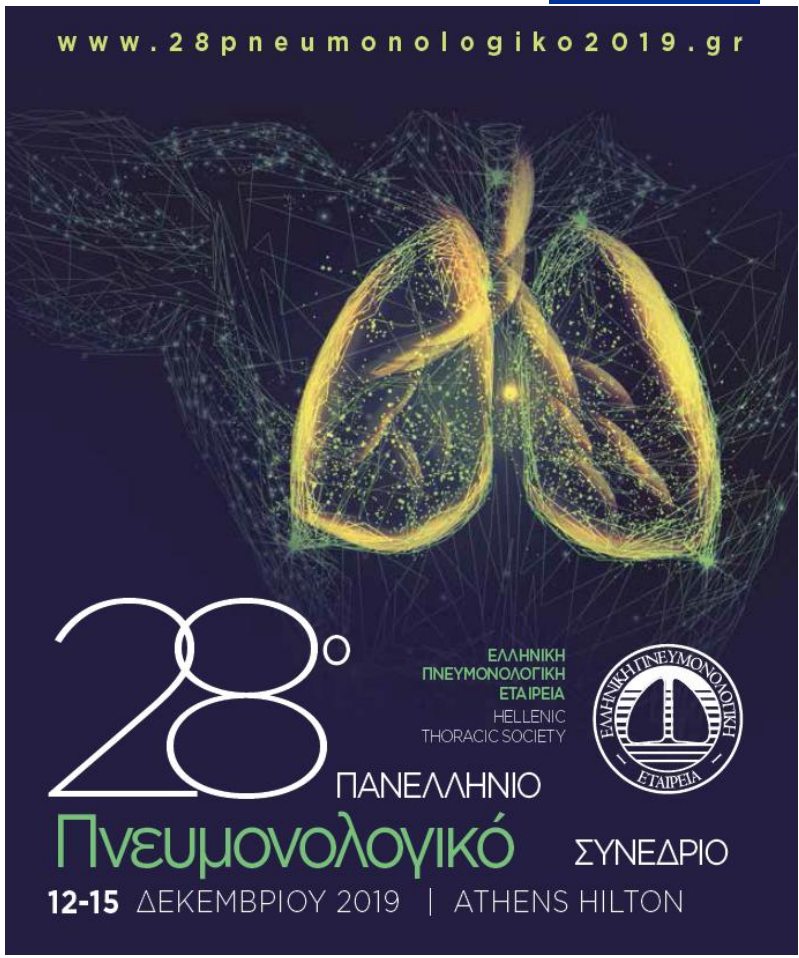
IPF pathogenesis

New Hypotheses

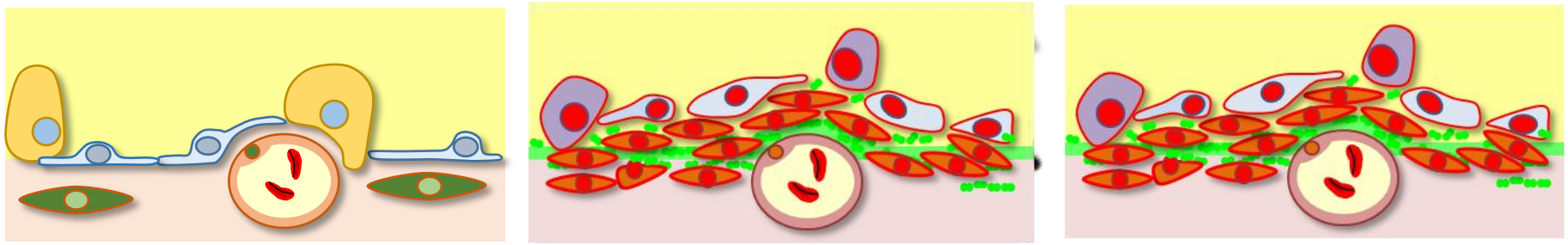


Argyris Tzouvelekis MD, MSc, PhD
Associate Professor of Pneumonology (elect)
University of Patras
argyrios.tzouvelekis@fleming.gr

“Old” concepts

Alveolar physiological state → **Usual Interstitial Pneumonia Lesion**

Recurring microinjuries → **Epithelial cells apoptosis** → **Epithelial & fibroblast activation** → **Matrix remodeling** → **Cell proliferation and migration**



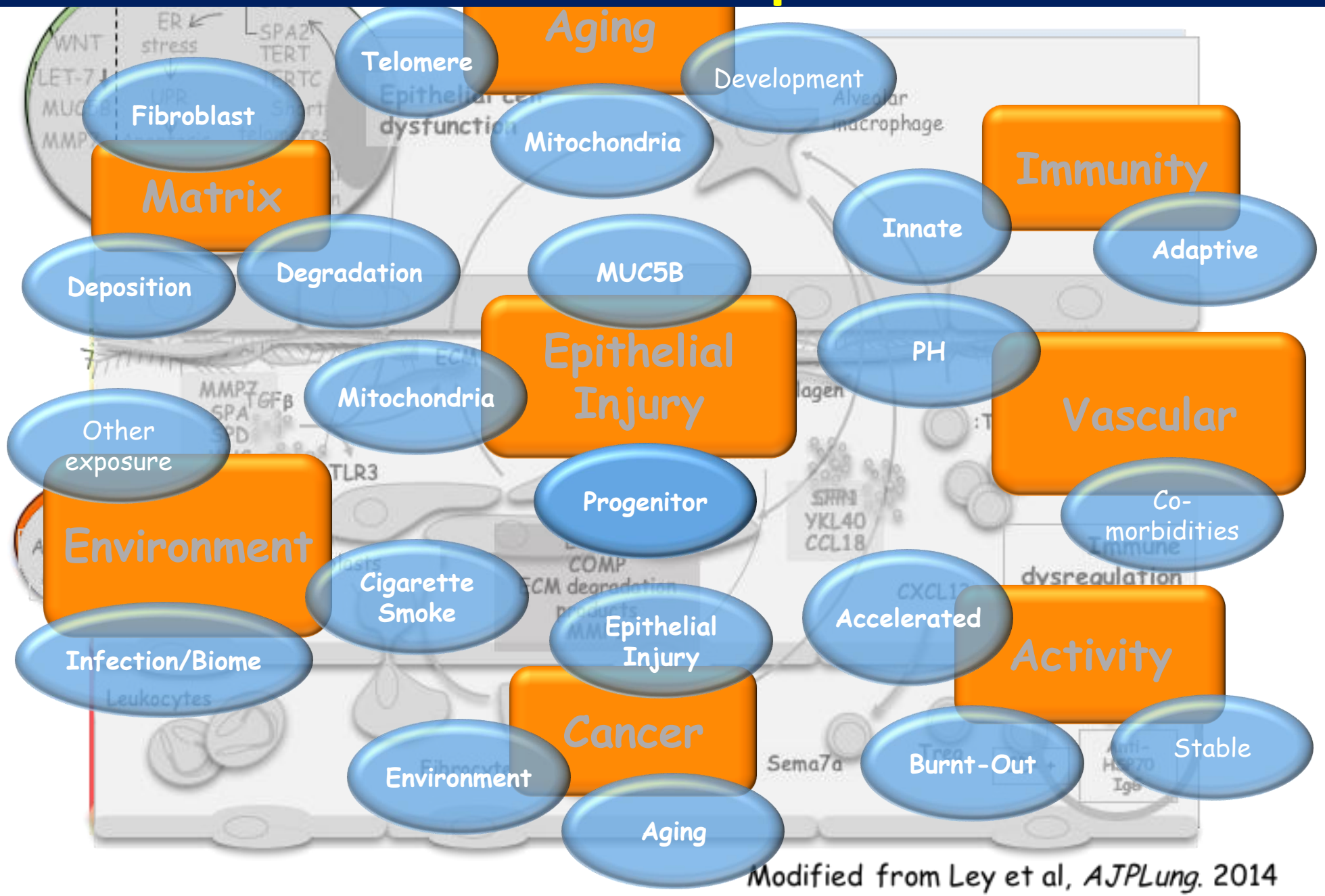
Pneumocyte type I

Pneumocyte type II

Endothelial cell

Fibroblast

New Concepts



Modified from Ley et al, *AJPLung*. 2014

“New” concepts

- Role of immune deregulation
- Role of aging – senescence
- Role of cellular bioenergetics
- Role of Microbiome/Gut-Lung axis
- The theory of basal epithelial stem cells

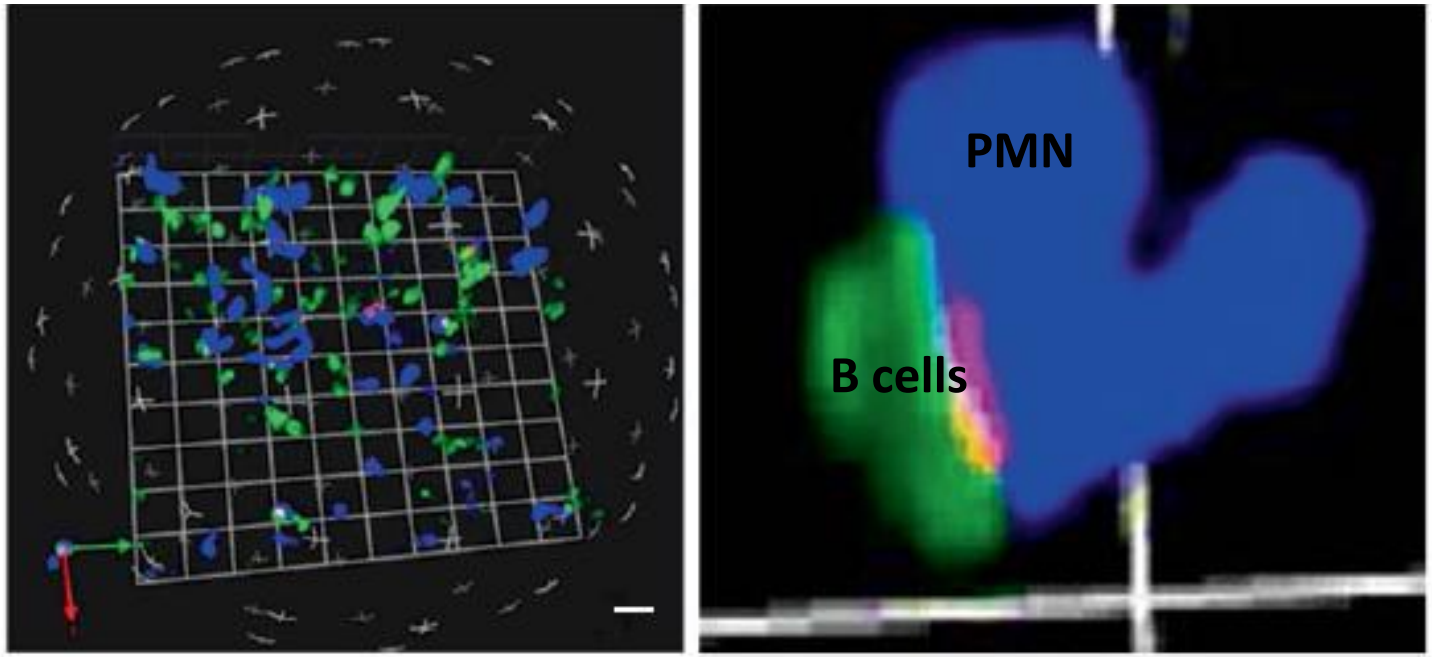
nature immunology

ARTICLES

https://doi.org/10.1038/s41590-017-0030-x

Aged polymorphonuclear leukocytes cause fibrotic interstitial lung disease in the absence of regulation by B cells

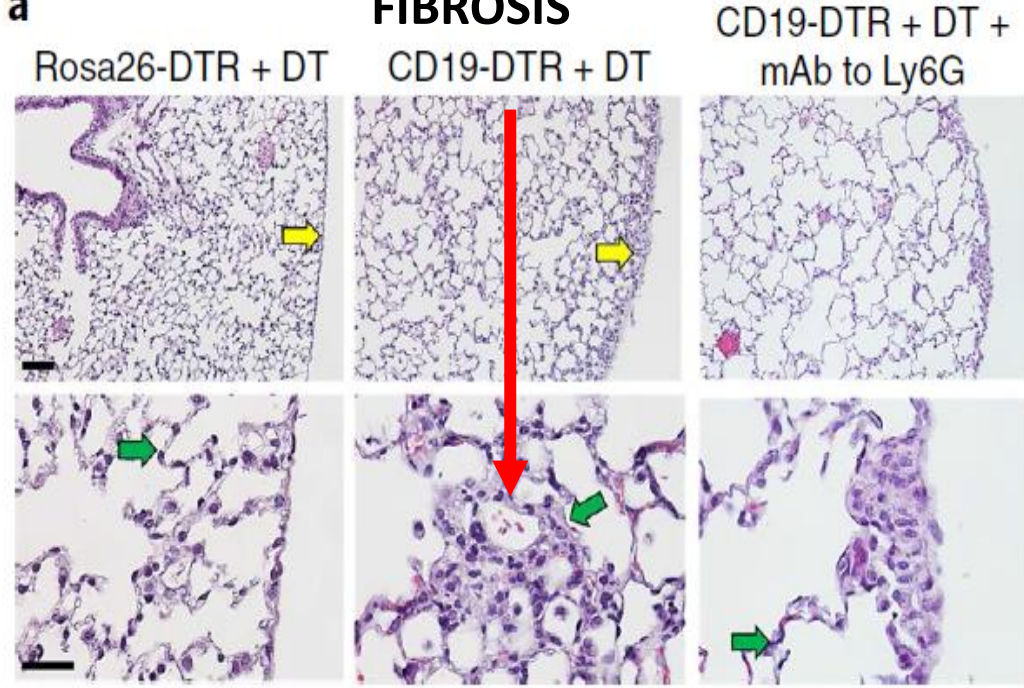
Jung Hwan Kim[1,2], John Podstawka[1,2], Yuefei Lou[1,2], Lu Li[1,2], Esther K. S. Lee[1,2], Maziar Divangahi[3], Björn Petri[4,5], Frank R. Jirik[6], Margaret M. Kelly[1,7] and Bryan G. Yipp[1,2*]



PMN B cell interaction

DEPLETED B CELLS

FIBROSIS

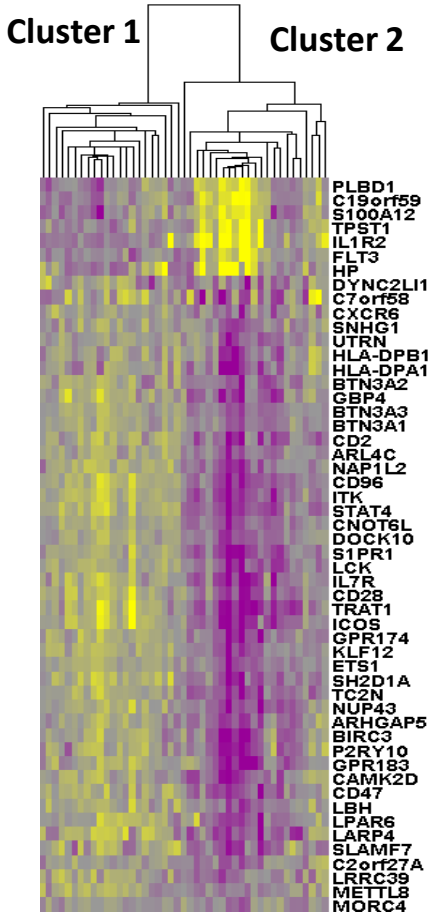


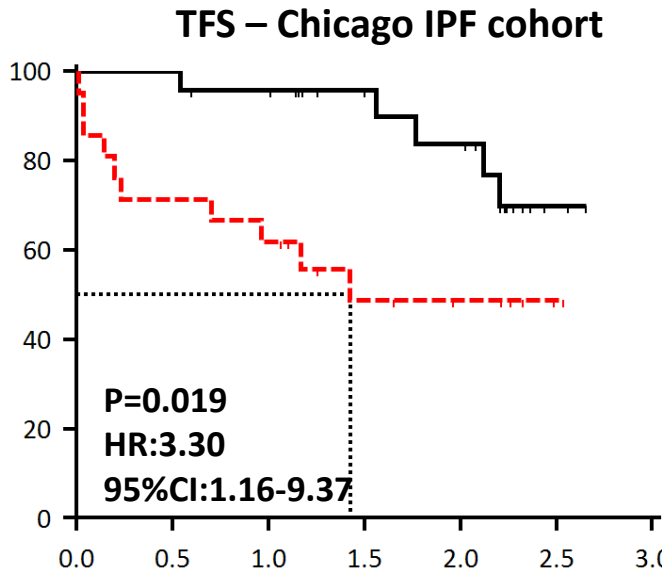
Validation of a 52-gene risk profile for outcome prediction in patients with idiopathic pulmonary fibrosis: an international, multicentre, cohort study

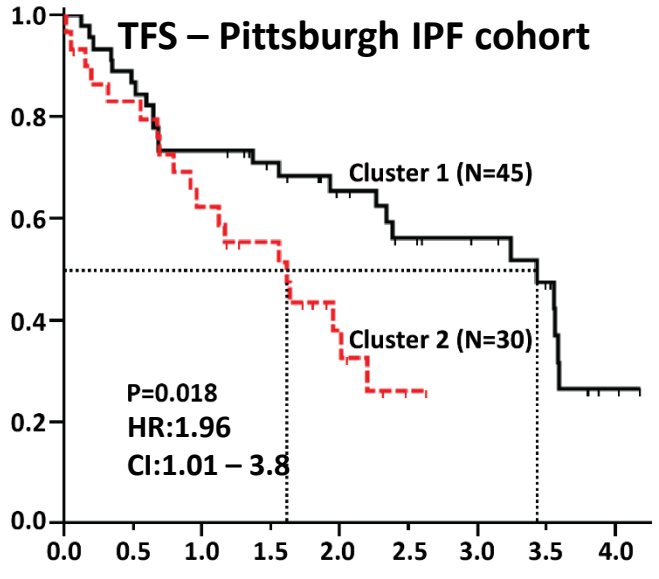
Jose D Herazo-Maya, Jiehuan Sun*, Philip L Molyneaux, Qin Li, Julian A Villalba, Argyrios Tzouvelekis, Heather Lynn, Brenda M Juan-Guardela, Cristobal Risquez, Juan C Osorio, Xiting Yan, George Michel, Nachelle Aurelien, Kathleen O Lindell, Melinda J Klesen, Miriam F Moffatt, William O Cookson, Yingze Zhang, Joe G N Garcia, Imre Noth, Antje Prasse, Ziv Bar-Joseph, Kevin F Gibson, Hongyu Zhao, Erica L Herzog, Ivan O Rosas, Toby M Maher, Naftali Kaminski*

Lancet Respir Med 2017

Published Online
September 20, 2017







Monocyte count – the ideal prognosticator?

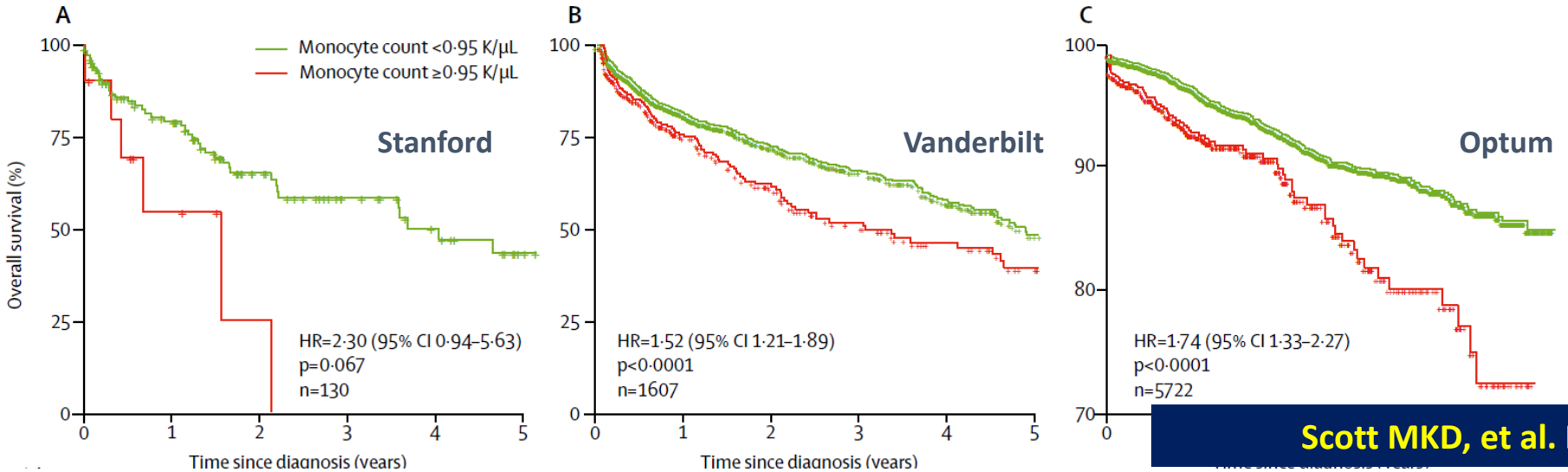
Increased monocyte count as a cellular biomarker for poor outcomes in fibrotic diseases: a retrospective, multicentre cohort study

Madeleine K D Scott, Katie Quinn, Qin Li, Robert Carroll, Hayley Warsinske, Francesco Vallania, Shirley Chen, Mary A Carns, Kathleen Aren, Jiehuan Sun, Kimberly Koloms, Jungwha Lee, Jessica Baral, Jonathan Kropski, Hongyu Zhao, Erica Herzog, Fernando J Martinez, Bethany B Moore, Monique Hinchcliff, Joshua Denny, Naftali Kaminski, Jose D Herazo-Maya, Nigam H Shah, Purvesh Khatri**

Finally we have a clinician-friendly, cheap biomarker

3 agents were approved in asthma based on Eos count

95% CI 1·22–3·47; p=0·0068) across the COMET, Stanford, and Northwestern datasets). Analysis of medical records of 7459 patients with idiopathic pulmonary fibrosis showed that patients with monocyte counts of 0·95 K/μL or greater were at increased risk of mortality with lung transplantation as a censoring event, after adjusting for age at diagnosis and



Scott MKD, et al. Lancet Respir Med 2019;7:497–508

Aging governs wound-healing response

- **Aging**-time-dependent functional decline of organs and tissues
- **Senescence**-irreversible cease of cell division
- Leading cause of death in Western civilization
- 100/150 K people across the globe die every day of age-related causes
- IPF incidence – 10/100.000
- IPF incidence >65 yrs – 90/100.000

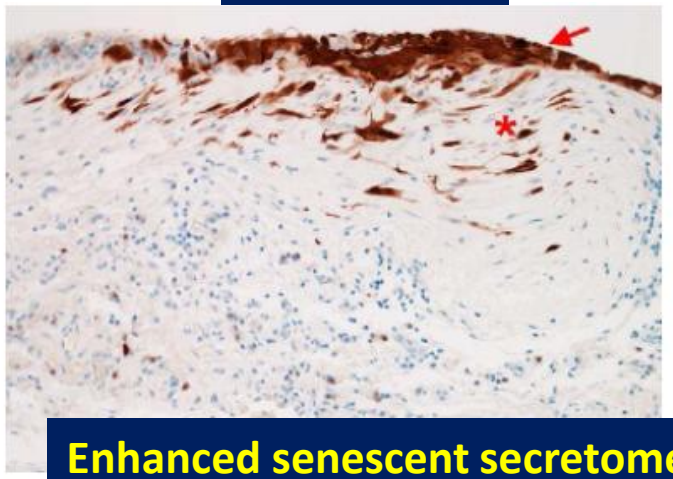
Received 6 Apr 2016 | Accepted 9 Jan 2017 | Published 23 Feb 2017

DOI: 10.1038/ncomms14532 OPEN

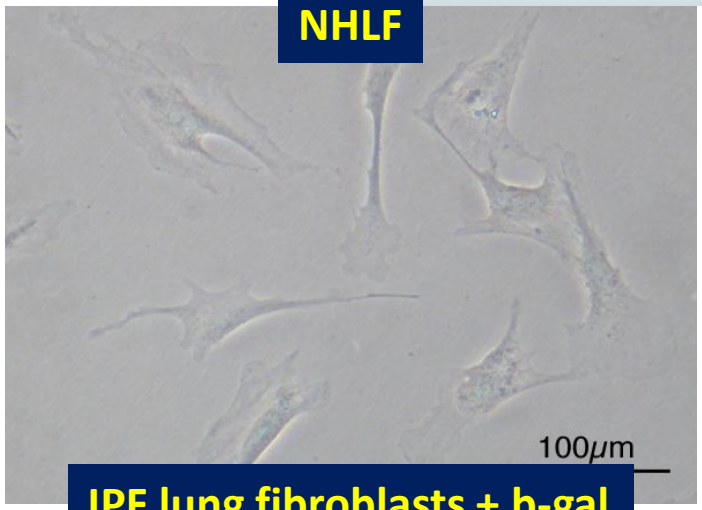
Cellular senescence mediates fibrotic pulmonary disease

nature COMMUNICATIONS

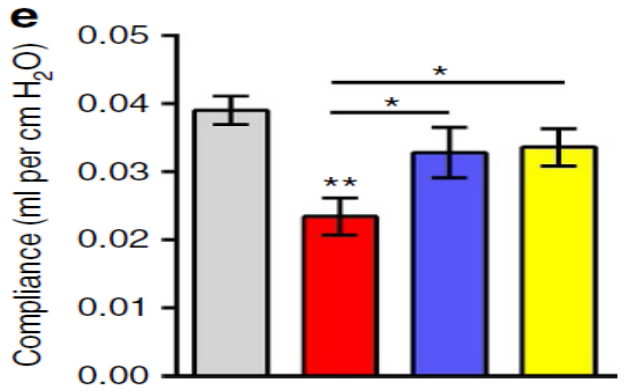
p16-IPF lung



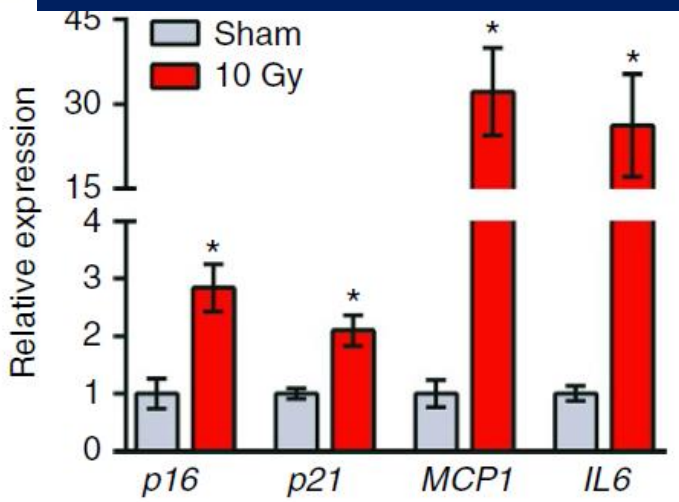
NHLF



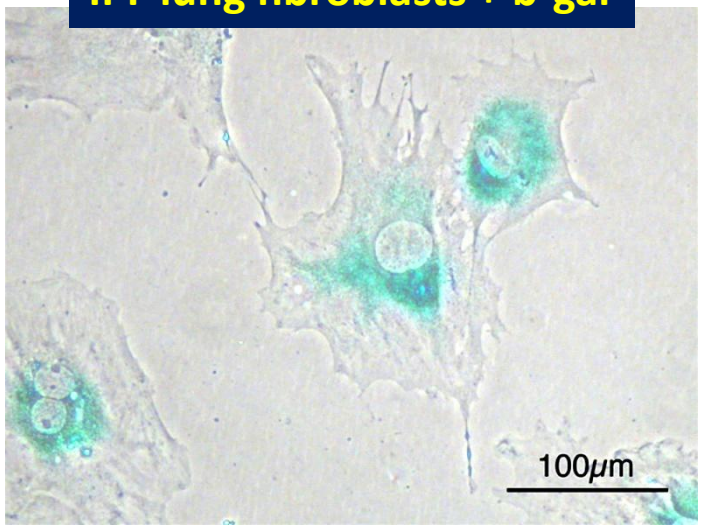
In-vivo anti-fibrotic effects of senolytics

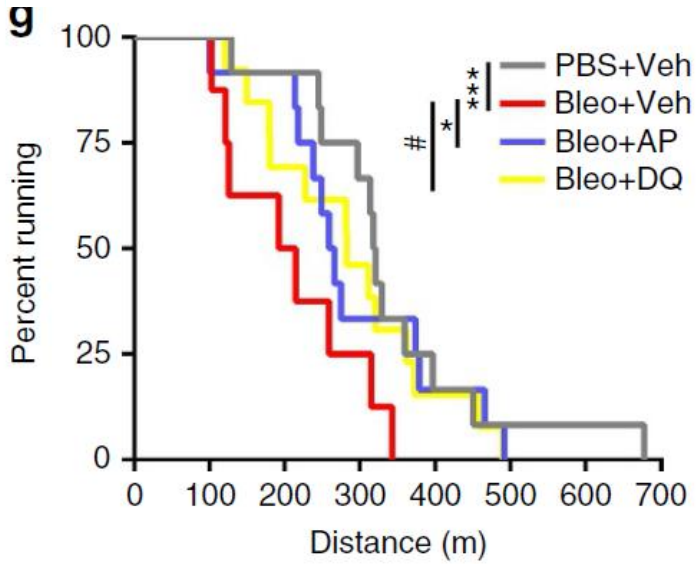


Enhanced senescent secretome



IPF lung fibroblasts + b-gal





Research paper

Senolytics in idiopathic pulmonary fibrosis: Results from a first-in-human, open-label, pilot study

EBioMedicine
Published by THE LANCET
Accepted 21 December 2018
Available online 5 January 2019

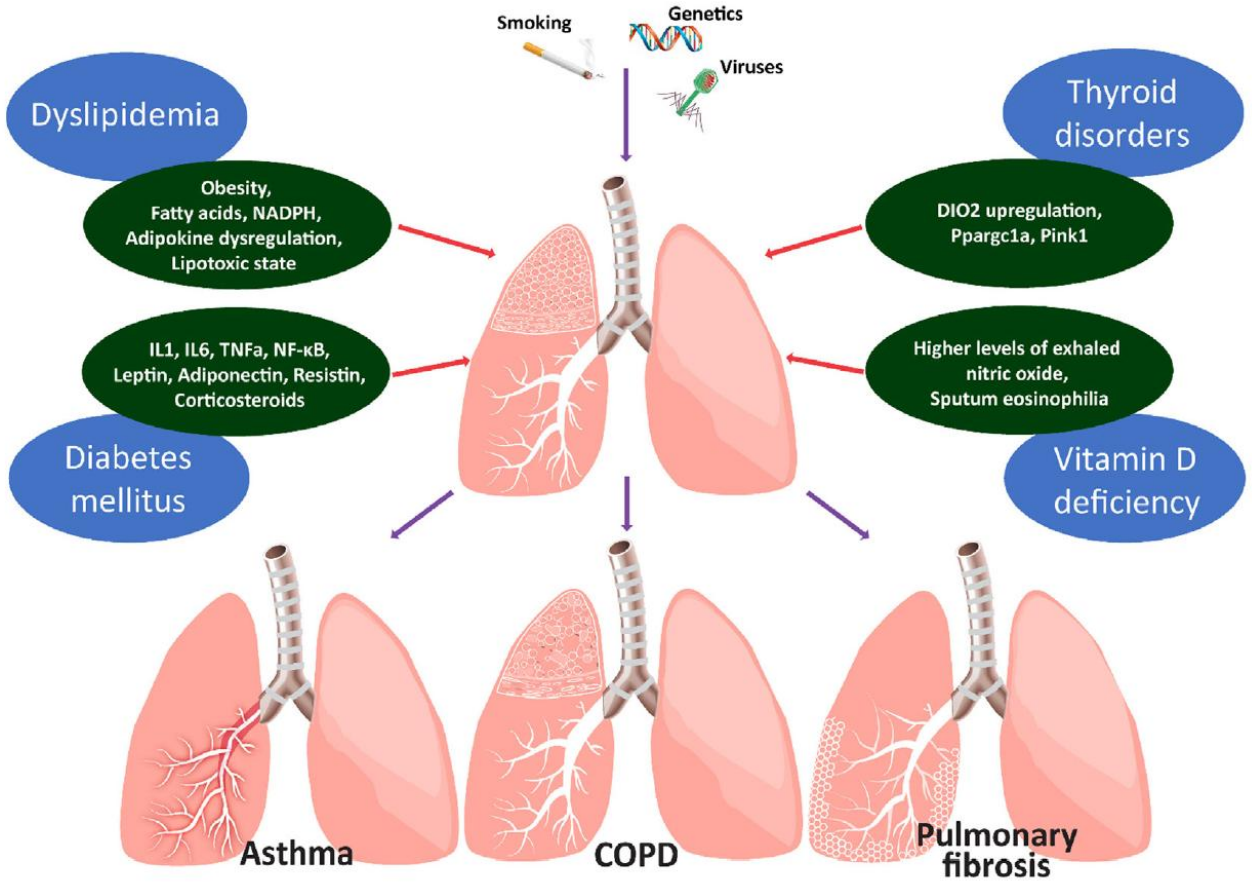
Jamie N. Justice [a,*,1], Anoop M. Nambiar [b,1], Tamar Tchkonia [c], Nathan K. LeBrasseur [c], Rodolfo Pascual [c], Shahrukh K. Hashmi [c], Larissa Prata [c], Michal M. Masternak [e], Stephen B. Kritchevsky [a], Nicolas Musi [f,g], James L. Kirkland [c]

Findings: Fourteen patients with stable IPF were recruited. The retention rate was 100% with no DQ discontinuation; planned clinical assessments were complete in 13/14 participants. One serious adverse event was reported. Non-serious events were primarily mild-moderate, with respiratory symptoms ($n = 16$ total events), skin irritation/bruising (n = 14), and gastrointestinal discomfort ($n = 12$) being most frequent. Physical function evaluated as 6-min walk distance, 4-m gait speed, and chair-stands time was significantly and clinically-meaningfully improved ($p < .05$). Pulmonary function, clinical chemistries, frailty index (FI-LAB), and reported health were unchanged. DQ effects on circulating SASP factors were inconclusive, but correlations were observed between change in function and change in SASP-related matrix-remodeling proteins, microRNAs, and pro-inflammatory cytokines (23/48 markers $r \geq 0.50$).

Metabolic Disorders in Chronic Lung Diseases

*Ourania Papaioannou[1], Theodoros Karampitsakos[2], Ilianna Barbayianni[3], Serafeim Chrysikos[2], Nikos Xylourgidis[3], Vasilis Tzilas[1], Demosthenes Bouros[1], Vasilis Aidinis[4] and Argyrios Tzouvelekis[1,4]**

REVIEW
published: 18 January 2018
doi: 10.3389/fmed.2017.00246



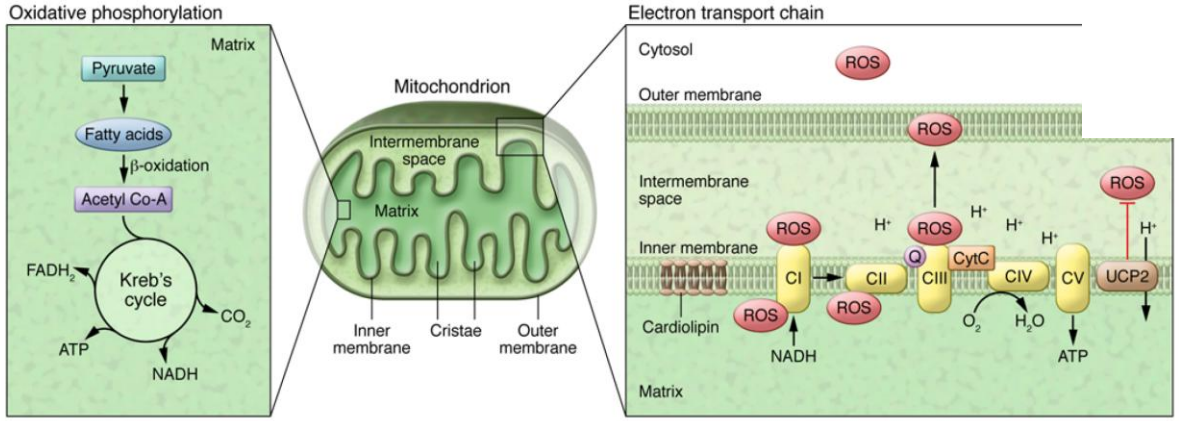
IPF, aging and cellular bioenergetics

The Journal of Clinical Investigation

Mitochondria in lung disease

Suzanne M. Cloonan and Augustine M.K. Choi

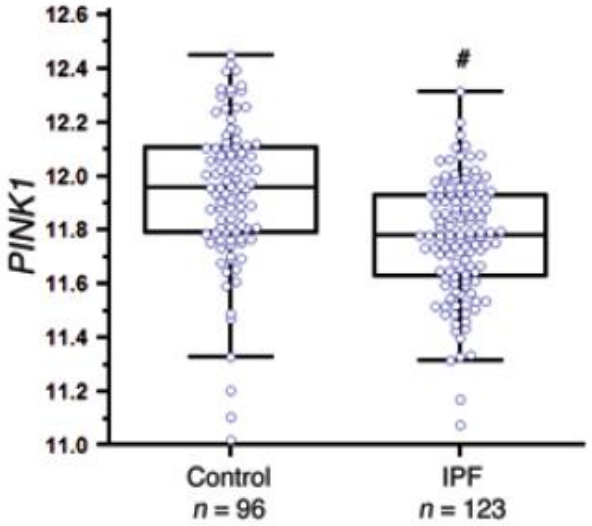
jci.org Volume 126 Number 3 March 2016

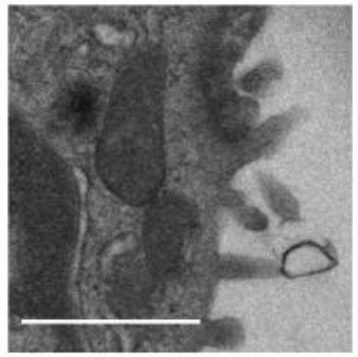


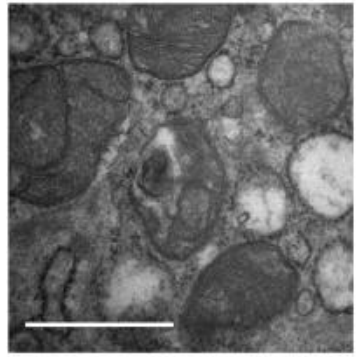
Mitochondria regulate cellular bioenergetics
Mitochondria regulate immune responses
Mitochondria regulate cell differentiation

AECIIs have >50% of total lung mitochondria

IPF aged lungs exhibit reduced PINK1 levels and damaged mitochondria





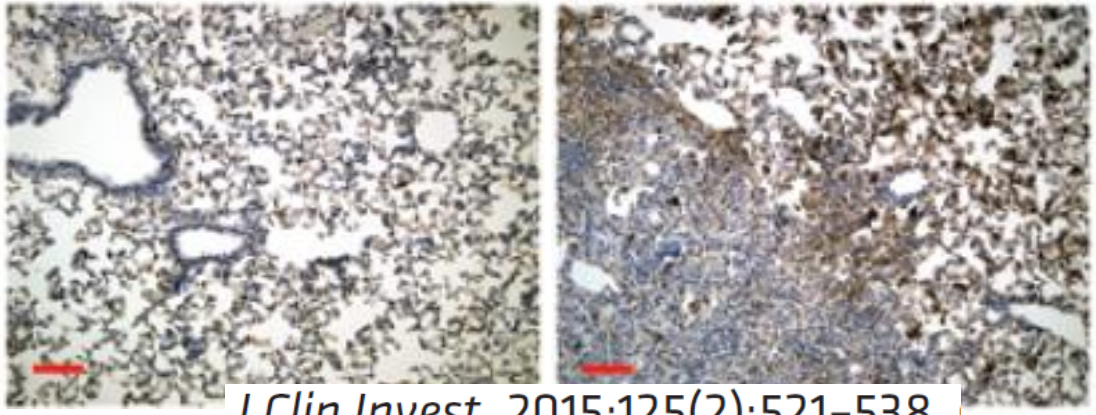


PINK1 -/- old mice exhibit enhanced lung fibrosis

Defective mitophagy and AEC apoptosis

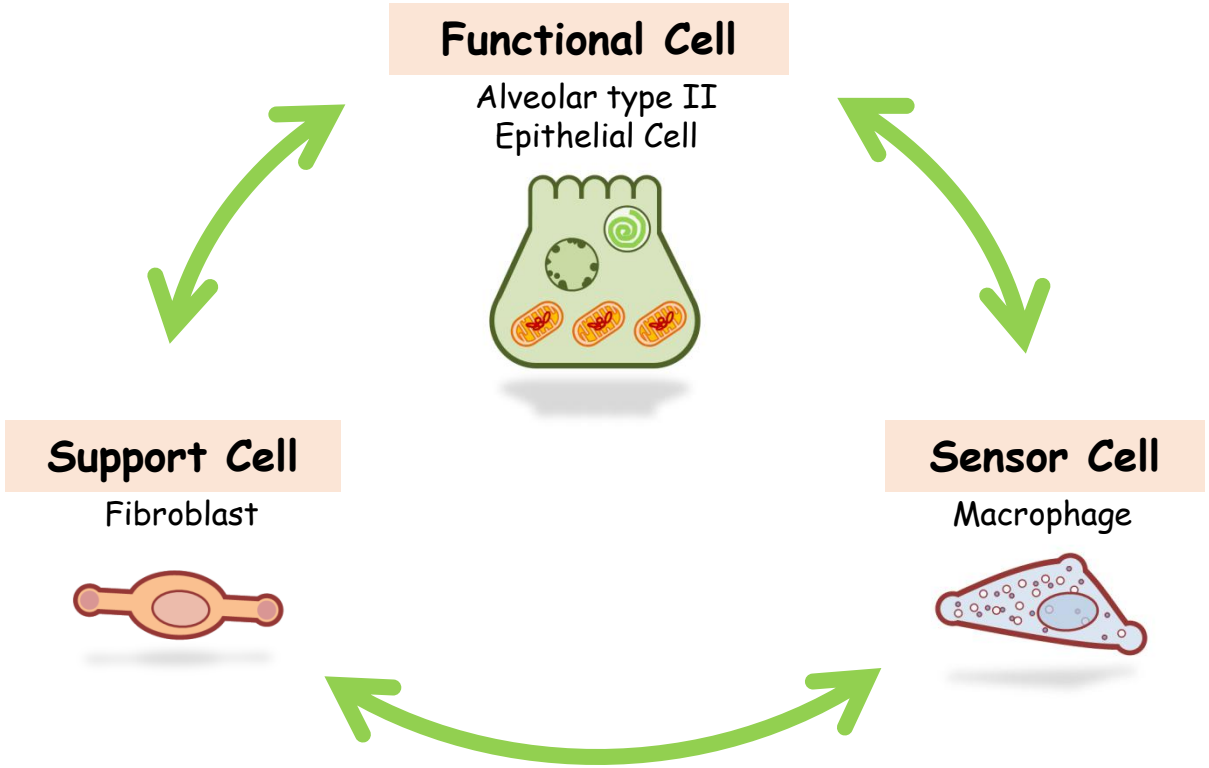
PINK1 +/+ **PINK1 -/-**

a-SMA

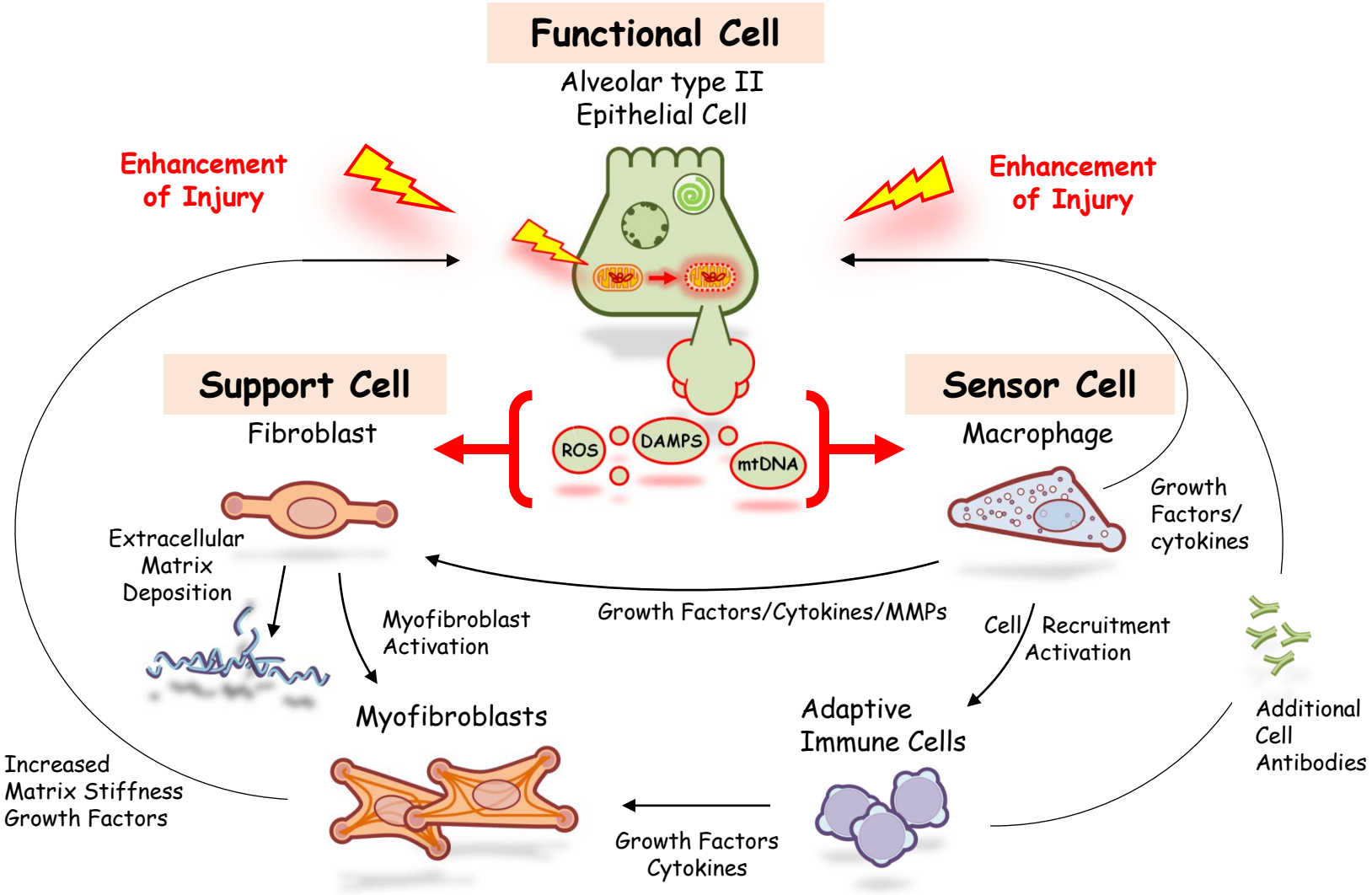


J Clin Invest. 2015;125(2):521–538.

The theory of functional cell protection

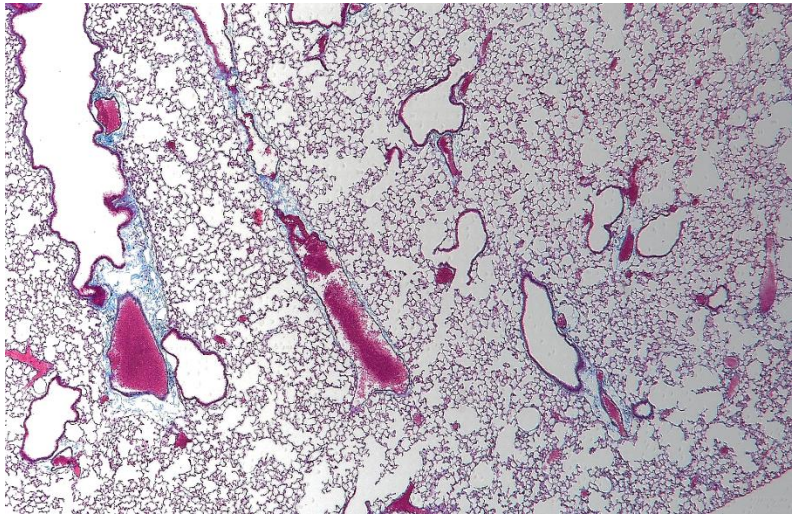


AECIIs drive disease pathogenesis

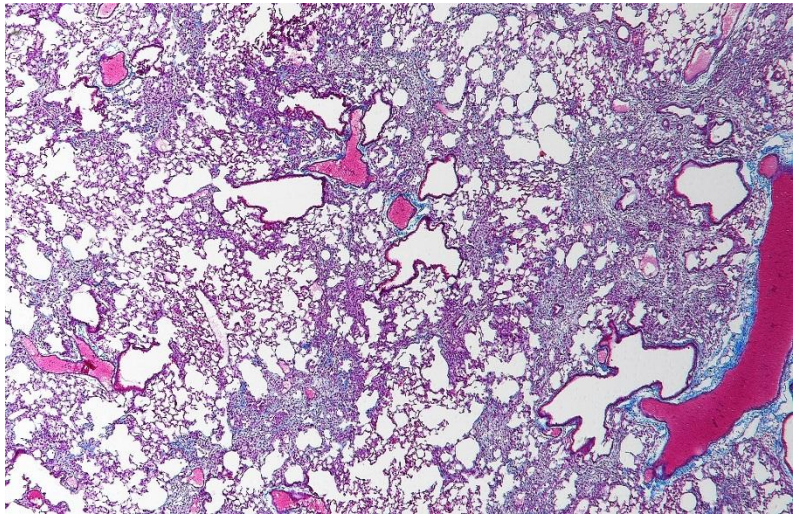


Aerosolized T3 attenuates bleomycin-induced established lung fibrosis

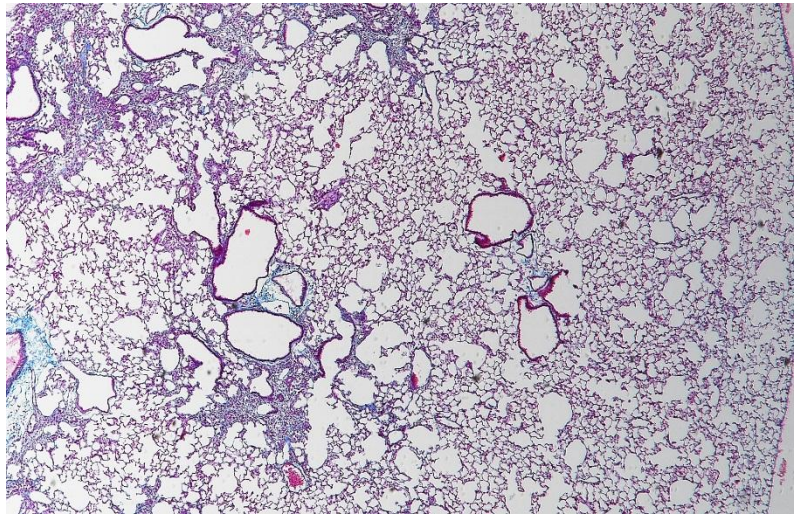
Saline



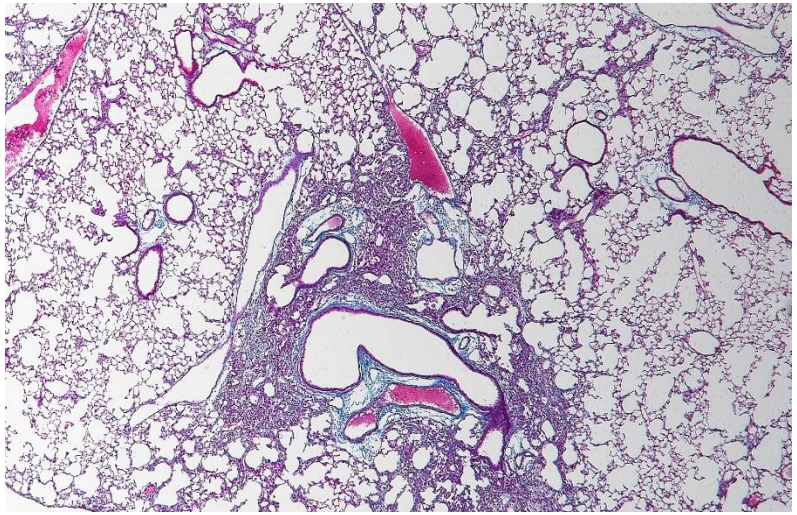
Bleo



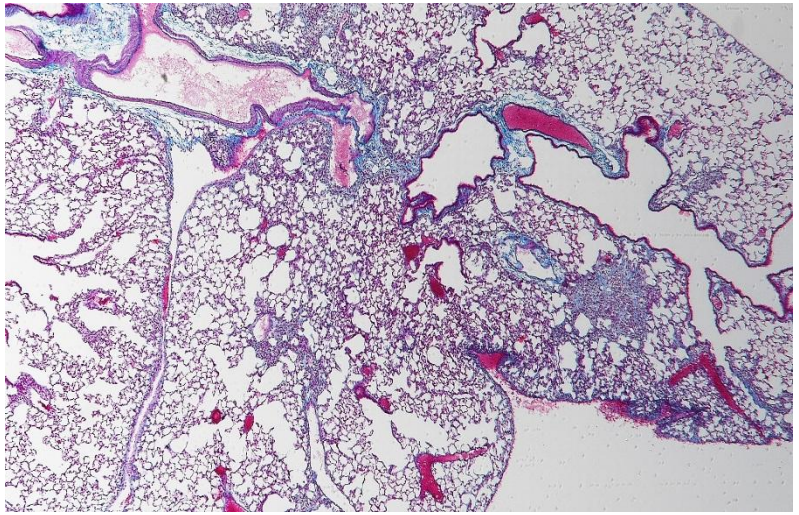
Bleo+T3 (Aerosolized)

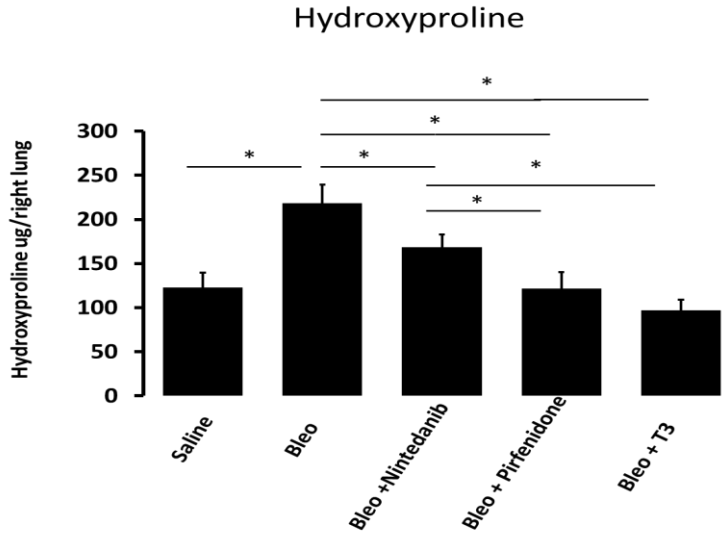


Bleo+Nintedanib



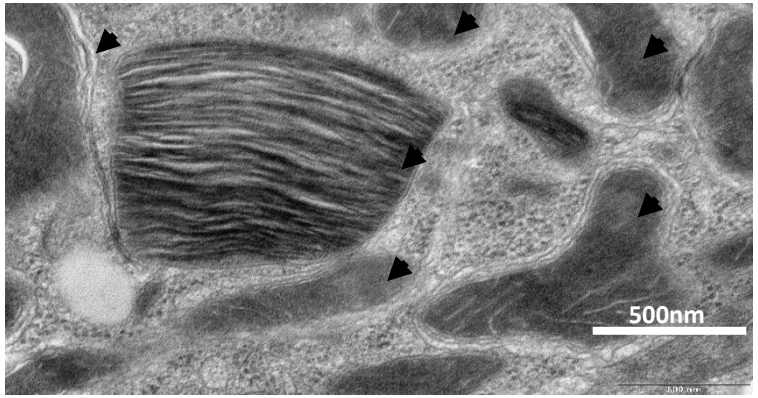
Bleo+Pirfenidone



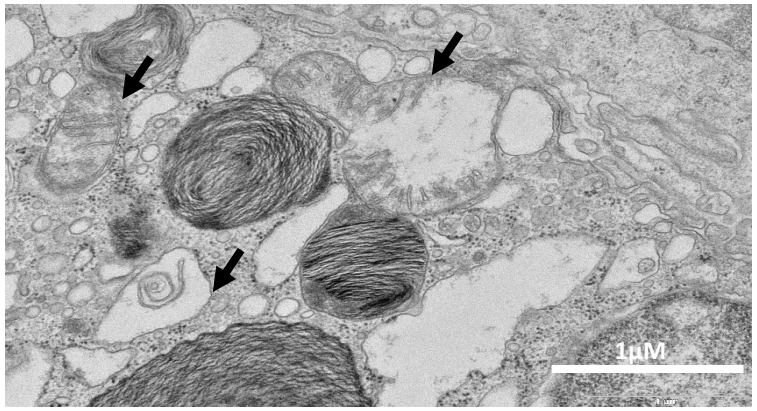


Aerosolized T3 improves BLM-induced mitochondrial abnormalities in AECIIs

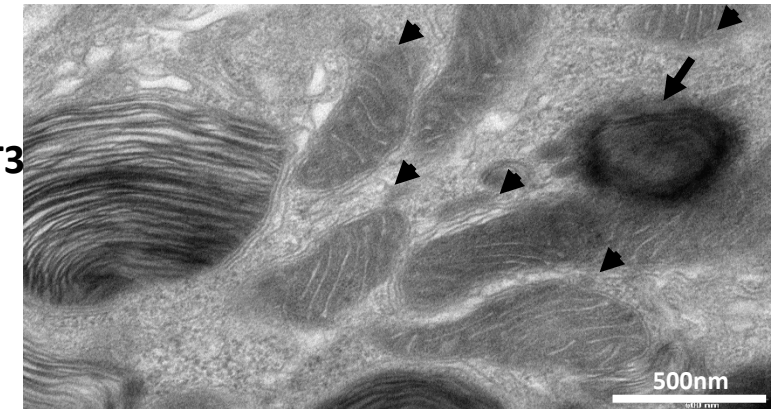
SALINE

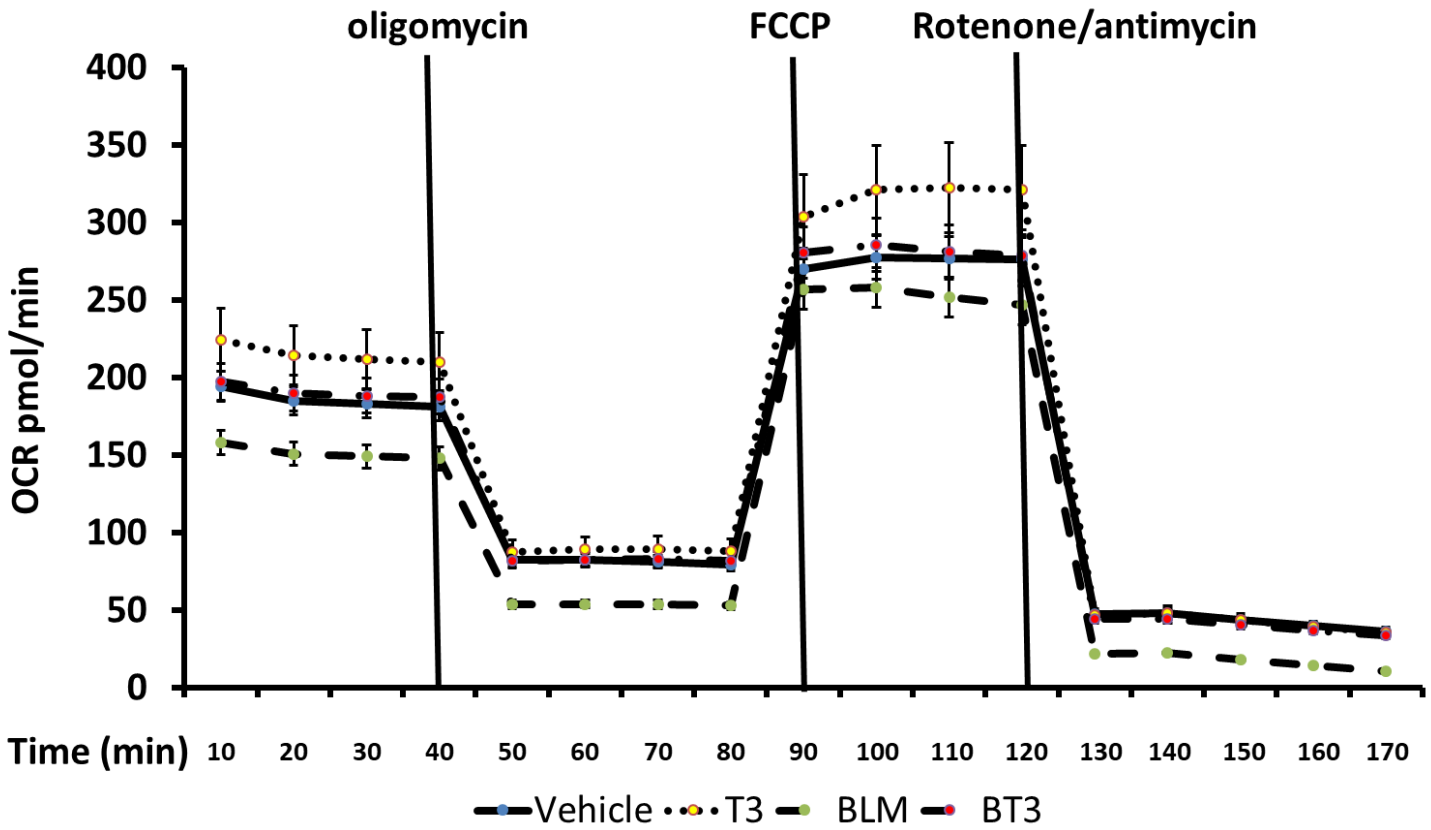


BLEOMYCIN

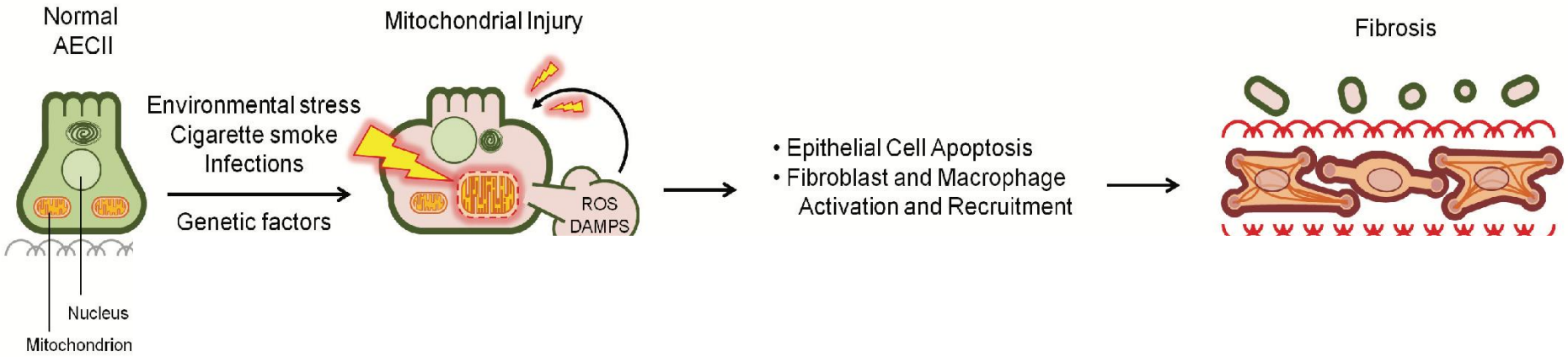


BLEOMYCIN + T3



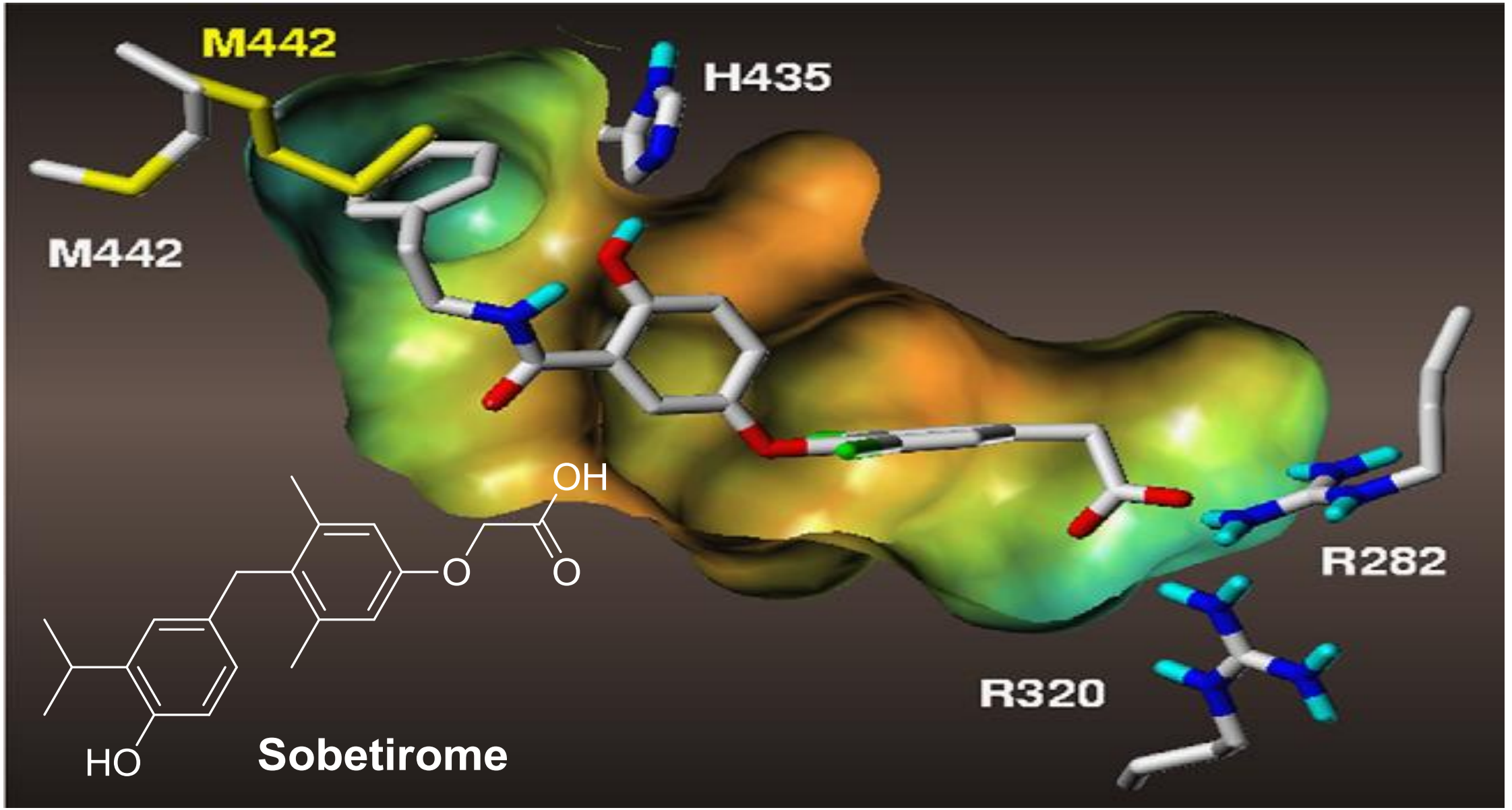


Thyroid Hormone agonists Reverse Pulmonary Fibrosis by Repairing Epithelial Cells

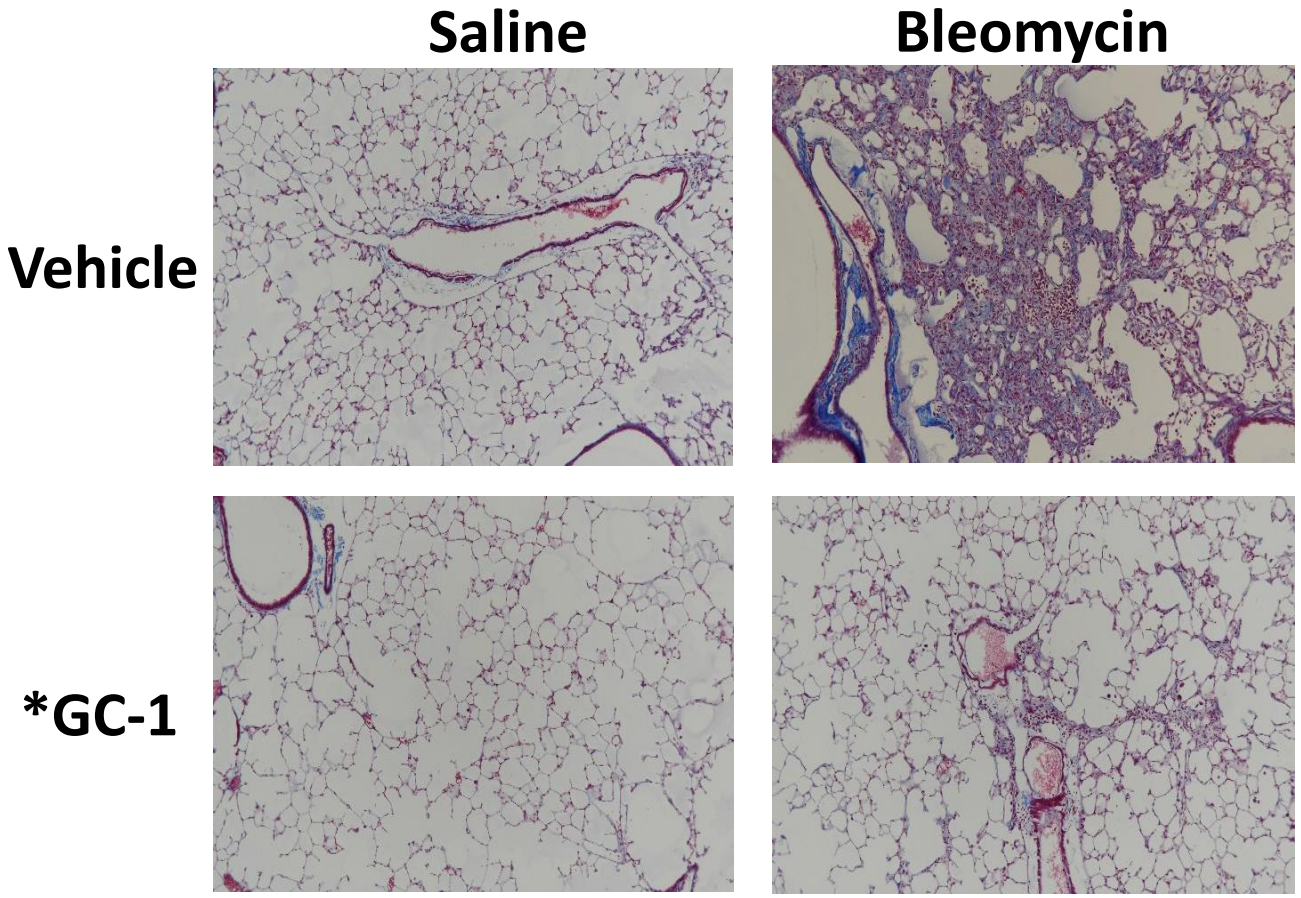


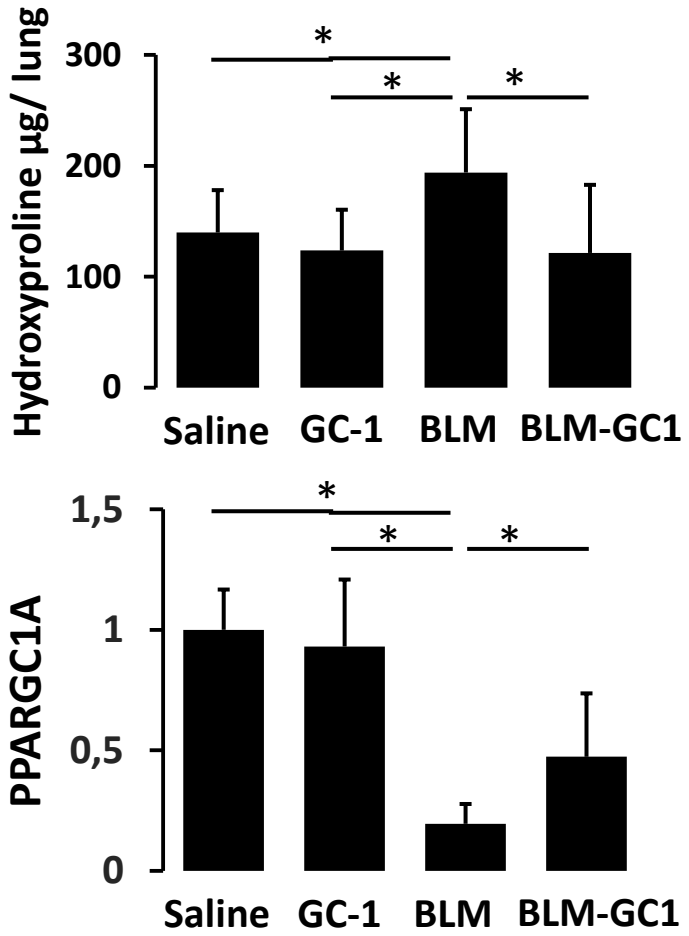
Yu, Tzouvelekis* et al.* Nature Medicine December 2017; https://www.nature.com/articles/nm.4447

Thyroid Hormone receptor –TRβ –unique structural properties



Sobetirome – GC1-attenuates BLM-induced lung fibrosis





*GC1-40ug/kg was administered orally at days 10,12,14,16,18. Mice were sacrificed at day 21 post bleomycin

ORIGINAL ARTICLE

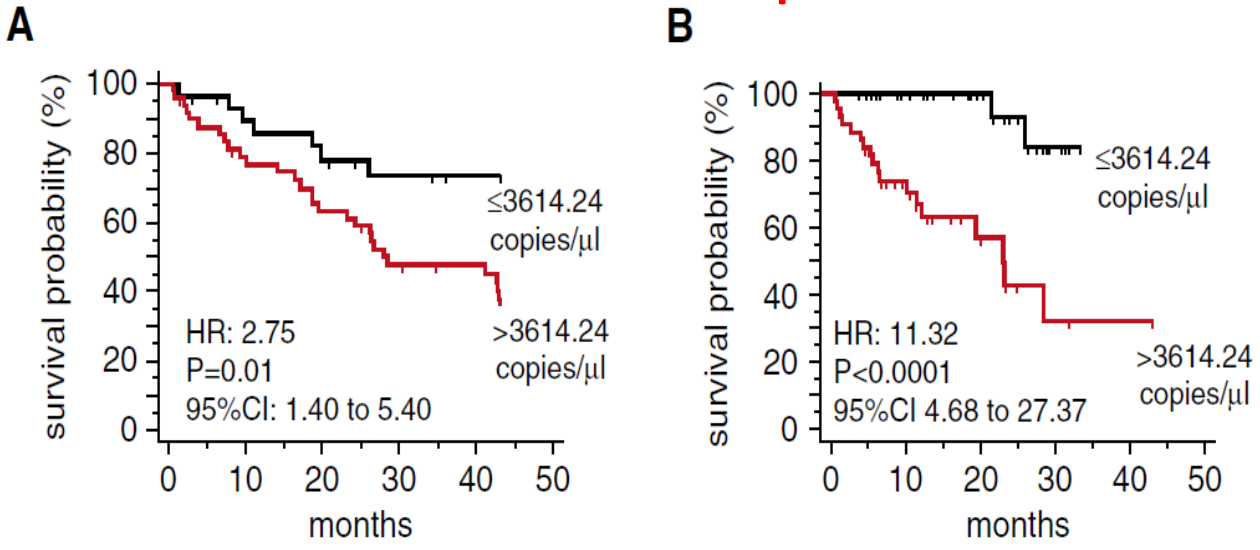
Extracellular Mitochondrial DNA Is Generated by Fibroblasts and Predicts Death in Idiopathic Pulmonary Fibrosis

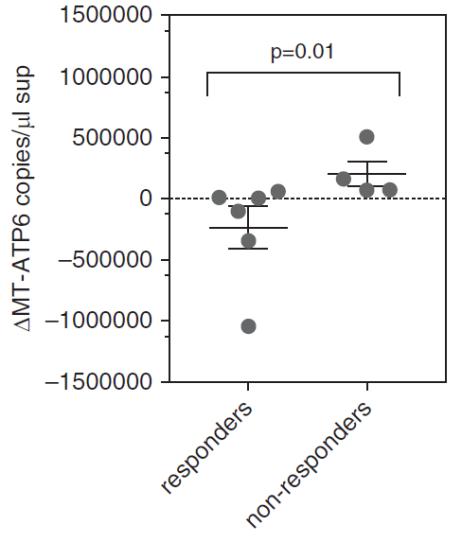
Changwan Ryu[1*], Huanxing Sun[1*], Mridu Gulati[1*], Jose D. Herazo-Maya[1], Yonglin Chen[2], Awo Osafo-Addo[1], Caitlin Brandsdorfer[1], Julia Winkler[1], Christina Blaul[1], Jaden Faunce[1], Hongyi Pan[1], Tony Woolard[1], Argyrios Tzouvelekis[1], Danielle E. Antin-Ozerkis[1], Jonathan T. Puchalski[1], Martin Slade[1], Anjelica L. Gonzalez[2], Daniel F. Bogenhagen[3], Varvara Kirillov[4], Carol Feghali-Bostwick[5], Kevin Gibson[6], Kathleen Lindell[6], Raimund I. Herzog[7], Charles S. Dela Cruz[1], Wajahat Mehal[8], Naftali Kaminski[1], Erica L. Herzog[1‡], and Glenda Trujillo[4‡]

Am J Respir Crit Care Med Vol 196, Iss 12, pp 1571–1581, Dec 15, 2017

Increased mtDNA correlates with poor survival

mtDNA correlates with pirfenidone response





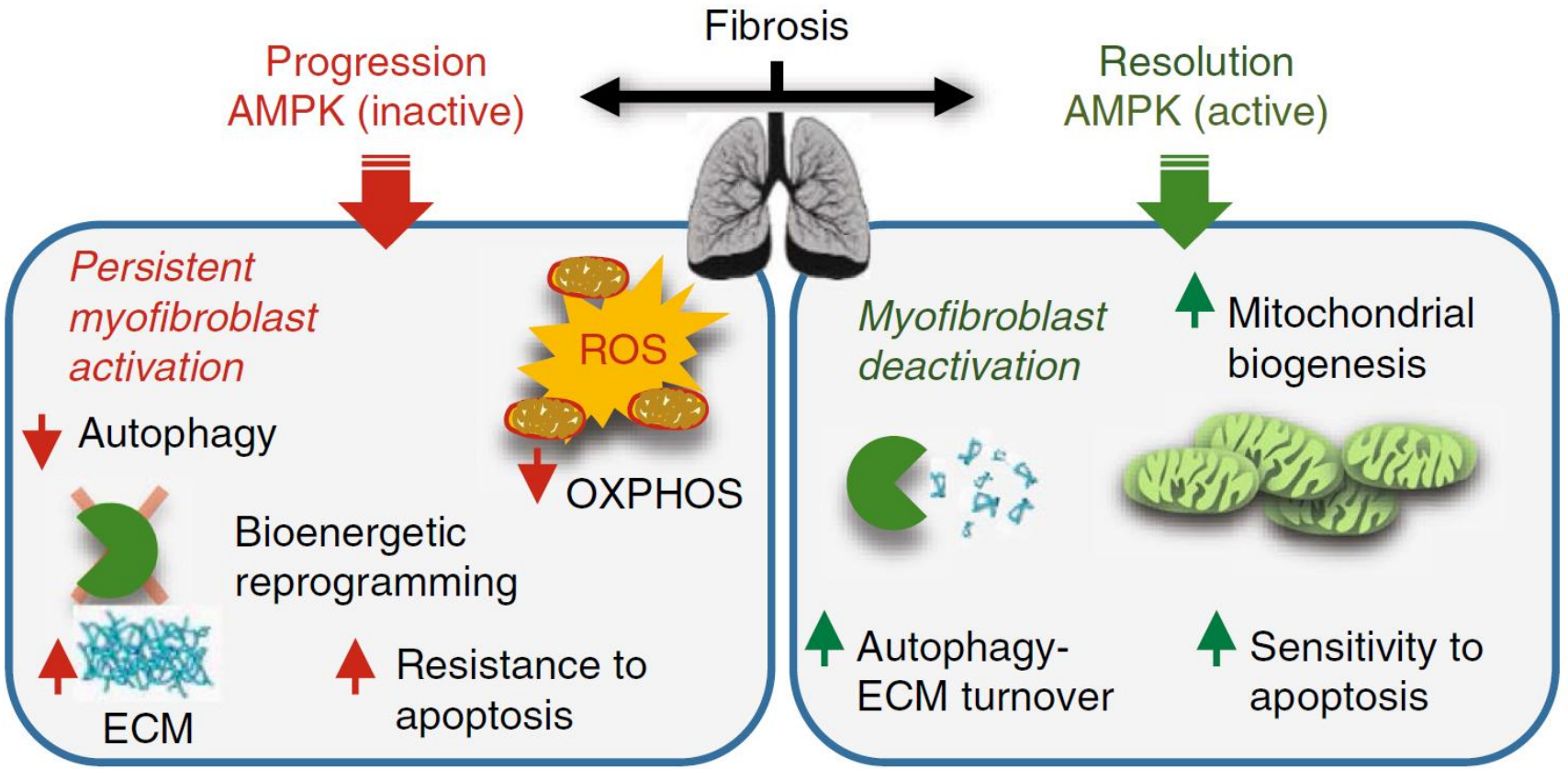
nature medicine

LETTERS

https://doi.org/10.1038/s41591-018-0087-6

Metformin reverses established lung fibrosis in a bleomycin model

Received: 9 August 2016; Accepted: 14 May 2018;
Published online: 02 July 2018

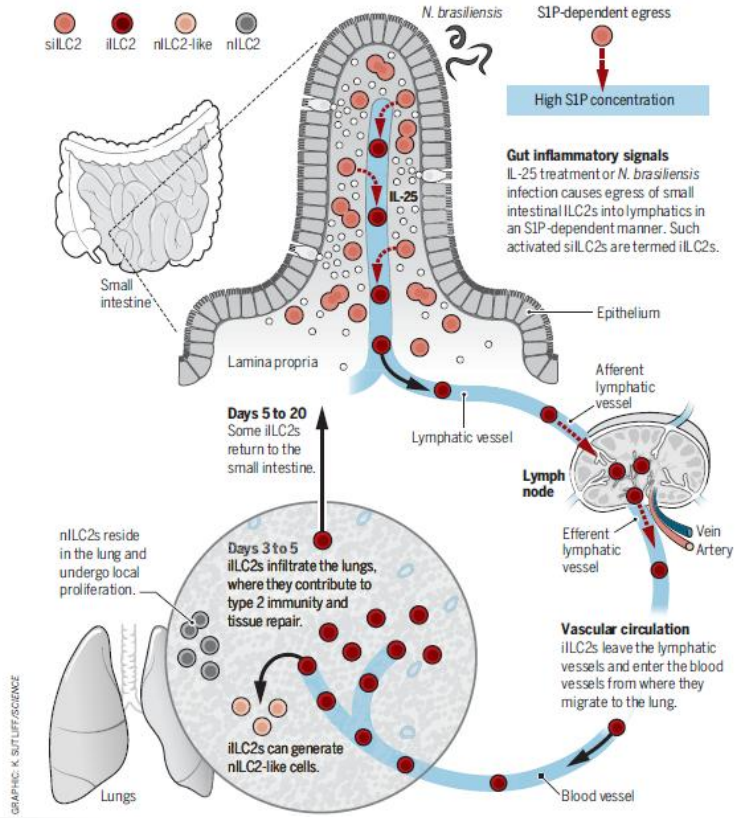


IMMUNOLOGY

Lung inflammation originating in the gut

Parasite infection in the intestine can lead to inflammatory immune cells in the lung

Huang *et al.*, *Science* **359**, 114–119 (2018) 5 January 2018



ORIGINAL ARTICLE

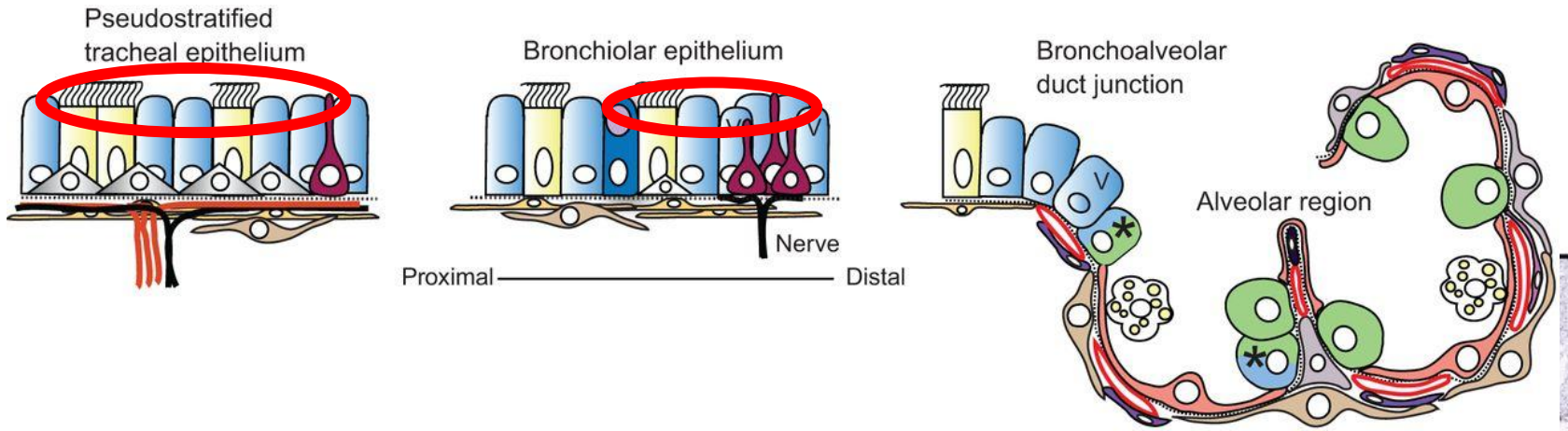
Host–Microbial Interactions in Idiopathic Pulmonary Fibrosis

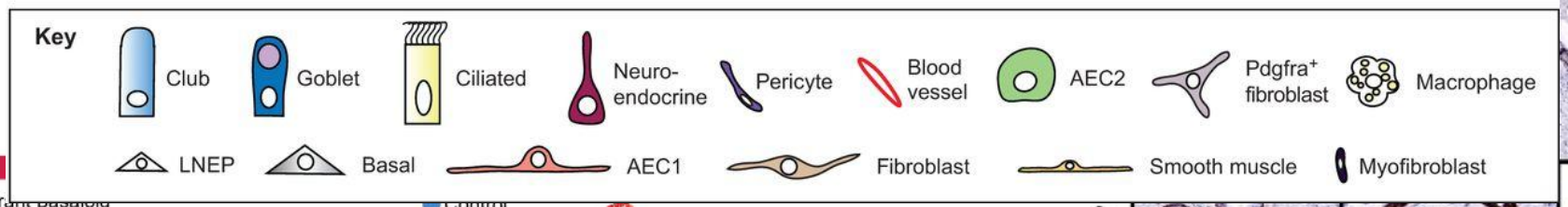
Philip L. Molyneaux[1,2], Saffron A. G. Willis-Owen[1], Michael J. Cox[1], Phillip James[1], Steven Cowman[1,2], Michael Loebinger[1,2], Andrew Blanchard[3], Lindsay M. Edwards[3], Carmel Stock[1,2], Cécile Daccord[1,2], Elisabetta A. Renzoni[1,2], Athol U. Wells[2], Miriam F. Moffatt[1]*, William O. C. Cookson[1,2]*, and Toby M. Maher[1,2]*

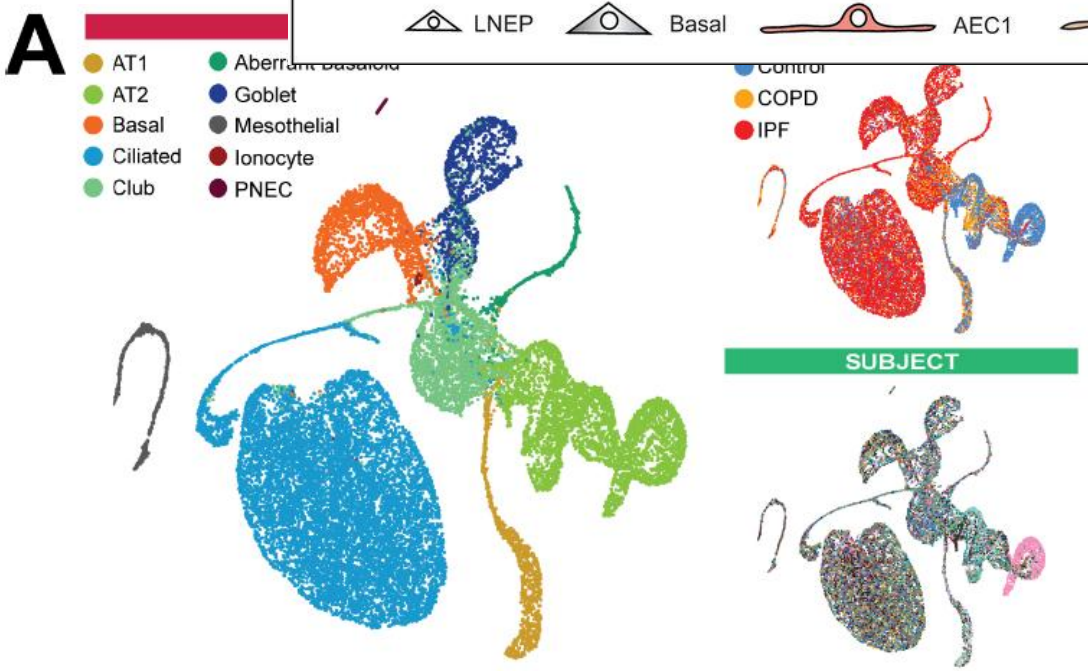
[1]National Heart and Lung Institute, Imperial College London, London, United Kingdom; [2]Royal Brompton Hospital, London, United Kingdom; and [3]Fibrosis Discovery Performance Unit, GlaxoSmithKline R&D, GlaxoSmithKline Medicines Research Centre, Stevenage, United Kingdom

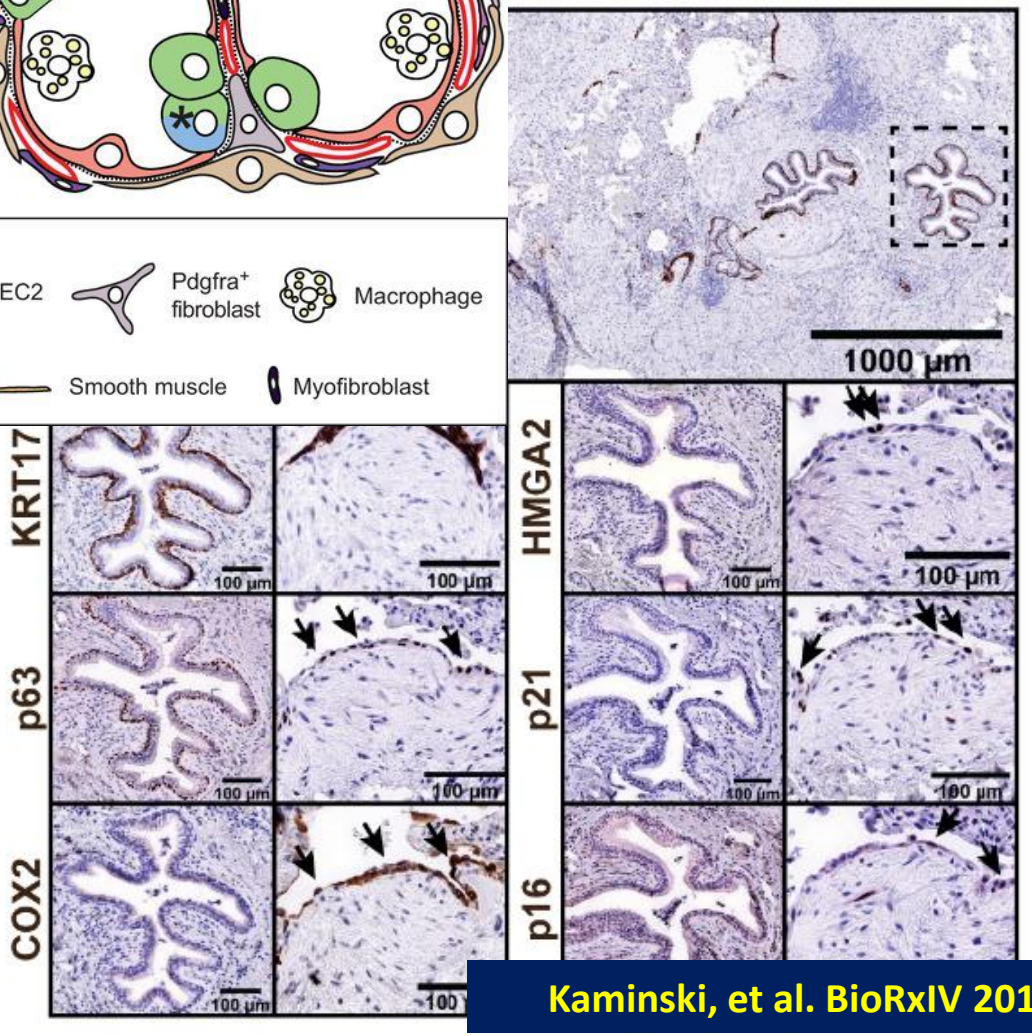
American Journal of Respiratory and Critical Care Medicine Volume 195 Number 12 | June 15 2017

Aberrant migration of basal stem cells to alveolar walls with potential pro-fibrotic role









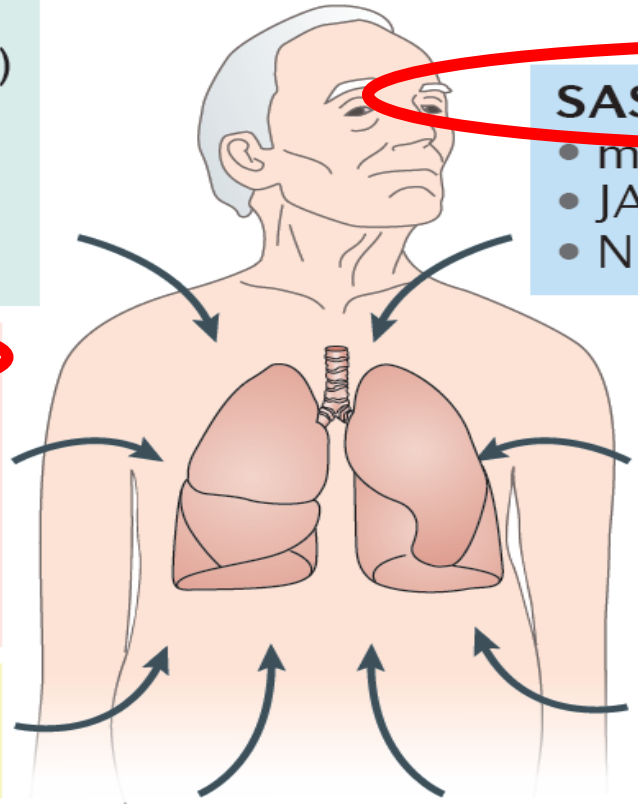
Kaminski, et al. BioRxIV 2019

Conclusions

Clearance of senescent cells
- Apoptosis inhibitor (navitoclax)
- Tyrosine kinase inhibitor (dasatinib)
- PI3K inhibitor (quercetin)
- p53 inhibitors
- Rupatadine
- NOX4 inhibitors

Mitochondria-targeted therapies
- Antioxidant scavengers
- SIRT3 agonist
- mtDNA repair enzymes
- Activators of mitophagy
- CD38 inhibitors

Activation of autophagy
- PI3K and mTOR inhibitors



SASP inhibition
- mTOR inhibitor (rapamycin)
- JAK or STAT inhibitors
- NF-κB inhibitors

Stem cell therapies
- Heterologous young donors

Targeting the epigenome
- 5′-azacytidine
- Antagomir miR-21
- HDAC inhibitor (vorinostat)

Activation of proteostasis
- Pharmacological chaperone
- Inhibitors of Ca^{2+} mobilization

Telomerase reactivation?

Ana L. Mora[1,2], Mauricio Rojas[1,3], *Nat Rev Drug Discov.* 2017 October 30;